The organization of motor maps in the human brain

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TITRE

The organization of motor maps in the human brain

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Résumé

Ce travail s'intéresse à l'organisation fonctionnelle du système sensorimoteur.

La somatotopie est une caractéristique essentielle de M1, mais l'organisation fonctionnelle des autres aires motrices (PM, SMA, et IPL) n'est pas encore clairement établie. Premièrement, nous avons exploré par IRMf l'organisation fonctionnelle sensorimotrice chez des sujets sains exécutant des mouvements simples. Nos résultats montrent que les représentations motrices sont organisées selon des synergies musculaires et qu'une organisation somatotopique, différente de celle de M1, existe dans l'IPL.

Bien qu'elle fasse régulièrement l'objet de critiques, la DES est à la base de la plupart de nos connaissances sur le cortex moteur, que confirme les études en IRMf. Ainsi, en réponse au débat en cours, nous avons passé en revue les arguments récents confortant la confiance que nous pouvons accorder à la DES.

Des études récentes concluent à l'implication du PPC dans l'intention motrice, mais le débat reste ouvert sur la relation entre intention et préparation motrices. Certains prétendent que l'intention serait le sous-produit de la préparation motrice, ne laissant aucune place à la volonté dans le contrôle moteur. Pour étudier cette question, nous avons mis en place une expérience comportementale, incluant des tâches de réaction simple et de Libet pour comparer les deux processus cognitifs. Nos résultats montrent que le temps de réaction entre intention interne et réaction motrice est égal à celui séparant commande externe et réaction motrice. Cela contredit donc l'affirmation selon laquelle la préparation motrice précèderait l'intention et donc que l'intention émergerait du processus d'intention motrice.

Mots clés: organisation fonctionnelle, somatotopie, cortex motrice primaire, cortex prémoteur, aire motrice supplémentaire, aire patrietale inférieure, intention motrice, préparation motrice, tâche de Libet, temps de réaction.

Summary

In this thesis, I am interested in the functional organization of human cortical sensorimotor system.

Somatotopy is the prominent structure of the functional organization in sensory and motor cortex. However, the structure of the functional organization in higher order motor area, such as IPL is little known. Therefore, in the first part, I study the functional organization of human sensory- and motor- related brain regions using fMRI, by guiding healthy subjects to perform simple repetitive movements of different body parts. Our results demonstrate that, 1) motor synergy is the neural basis represented in the motor cortex; and 2) somatotopic organization also exists in IPL but with different structure from that of sensorimotor cortex.

Despite continuous criticism on DES, most of our primitive knowledge of the sensorimotor cortex comes from DES studies, and our fMRI result supports the findings of DES. In response to the ongoing debate on DES, in the second study, we review recent evidence to re-establish the confidence on DES.

Accumulating evidence indicates that PPC is related to the emergence of motor intention. However, debate on the relation between motor intention and preparation never stops, some claims that motor intention is the byproduct from motor preparation, thus denying the volition of human motor control. Besides this complexity, we design a straightforward behavior experiment, including simple reaction task and Libet task, in order to compare the cognitive process of motor preparation and motor intention. Our result shows that RT from internal motor intention to motor output is equal to the RT from external cue to motor output, thus rejecting the possibility that motor preparation starts in advance of motor intention and doesn't support that motor intention arises from the process of motor intention.

Key words: functional organization, somatotopy, primary motor area, premotor cortex, supplementary motor area, inferior parietal area, motor intention, motor preparation, Libet task, reaction time.

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List of abbreviations

Brain regions

M1: Primary motor cortex

4a : Anterior area 4

4p : Posterior area 4

PM : Premotor cortex

SMA : Supplementary motor cortex

PPC : Posterior parietal cortex

SPL: Superior parietal lobule

IPL: Inferior parietal lobule

IPS: Intraparietal sulcus

Other abbreviation:

PET: Positron emission tomography

fMRI: Functional magnetic resonance imaging

DES : Direct electrical stimulation

ICMS : Intra-cortical micro-stimulation

ROI : Region of interest

CNS: Central Nervous System

Chapter I. Theoretical background

The highest level in the human sensorimotor system occupies several macro-anatomical regions of the cerebral cortex, which contains the primary motor cortex (M1)(Sanes and Donoghue, 2000)(Graziano et al., 2002)(Aflalo and Graziano, 2007), the premotor cortex (PM)(Graziano et al., 1994; Wiesendanger, 2011)(Graziano and Cooke, 2006), the supplementary motor area (SMA)(Tanji, 1994), the cingulate motor area (CMA)(Dum and Strick, 1993; Paus, 2001; Shima and Tanji, 1998), the posterior parietal cortex (PPC), (Mattingley et al., 1998)(Aflalo et al., 2015; Cui and Andersen, 2007; Desmurget et al., 1999; Fernandez-Ruiz et al., 2007; Thoenissen et al., 2002), as well as the cerebellum(Schmahmann et al., 1999)(Mottolese et al., 2013; van der Zwaag et al., 2013).

The primitive evidence of functional specificity in the brain derives from the study by Fritsch and Hitzig in 1870s on the motor cortex of canine (York and Steinberg, 2011). Their pioneering work demonstrates the electrical excitability of cerebral cortex, which could generate muscle twitches by directly delivering electrical stimulation on it. The functional localization in human cerebral cortex, a fundamental research direction in cognitive neuroscience, dates back to the study by Ferrier (Ferrier, 1873) . Thanks to the improvement of electrical stimulation technique, more and more evidence of functional localization emerges, not only on that of motor cortex (Penfield and Boldrey, 1937), but also on visual (Humayun MS et al., 1996)(Brindley and Lewin, 1968), and language-related brain regions (Ojemann et al., 2009)(Ojemann, 1983)(Kim et al., 1997).

The systematical examination of human motor and sensory cortex by Penfield and his colleagues extradinarily advanced our understanding on the functional organization of cerebral cortex (Penfield and Rasmussen, 1950). Following their work, for a long time, movement was considered as the motor unit being represented in the sensorimotor cortex (Kakei et al., 1999). Until recently, the neural basis of functional organization in cortical sensorimotor cortex with respect to the complex musculoskeletal system is still under debate.

Nowadays, in primate, studies at more micro-level starts to provide more solid and direct evidence on the innervation of muscular system from central nervous system (CNS) (Rathelot and Strick, 2009). Recently, neural imaging technique gives access to non-invasively study brain functions with healthy subjects, in both lower sensory and motor processing related brain areas,

such as somatomotor, somatosensory and primary visual cortex, and higher cognitive brain areas, such as prefrontal cortex and parietal cortex (Brett et al., 2002).

I.1 The functional organization of M1: its structure and neural basis

I.1.1 Somatotopic organization in M1

The functional organization in M1 has a prominent feature, termed as somatotopy by neuroscientists. It implies that the functional localization of each body part follows its sequential order of the body schema. In 1870s, the neurologist John Hughlings Jackson initially observes somatotopy on epileptic patients. He notices that that epileptic patients always has convulsions beginning unilaterally and spreading orderly, for example, if the seizure begins in face, it would spread to arm then leg sequentially, but never in reversed order (York and Steinberg, 2011).

Half a century later, Canadian neurosurgeon Penfield and his colleagues propose a more systematic illustration of the somatotopic structure in motor and sensory cortex with a large sample of patients (Penfield and Boldrey, 1937)(Penfield and Rasmussen,1950). In their pioneering work, multiple electrodes are planted along the precentral gyrus (PrG), postcentral gyrus (PoG) in the brain of epileptic patients. And by delivering electrical stimulation at each electrode site one by one, they could observe the muscular responses or ask the awaking patients to report their sensational feeling **(Figure 1).** With this procedure, they are able to map different body parts to corresponding sites on the sensorimotor cortex, which demonstrates the specific localization of motor or sensory function on the cortical surface. Within Penfield's illustration, functional localization of different body parts are arranged along the ribbon of PrG and PoG in somatotopic order. For example, tongue and foot representations lie on the most ventral and dorsal part respectively, whileas face and hand representations are in-between. Also, the zone of functional representation is not proportional to the surface of body part, such as that face and hand representations are emphasized to be significantly larger than those of arm, leg and foot; similarly, within the hand region, thumb representation is comparatively larger than that of any other finger. In this way, Penfield's illustration is figuratively called the 'homunculus' **(Figure 2).**

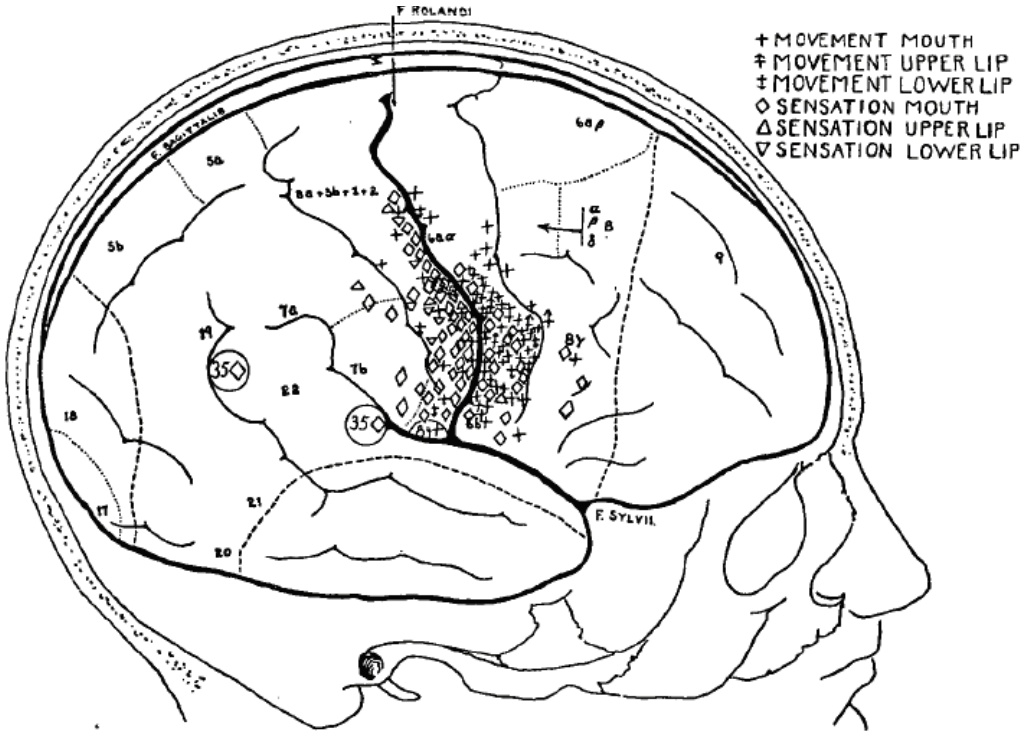

Figure1. **An illustration of the stimulation sites in the brain of one patient. From Penfield and Boldrey, 1937.**

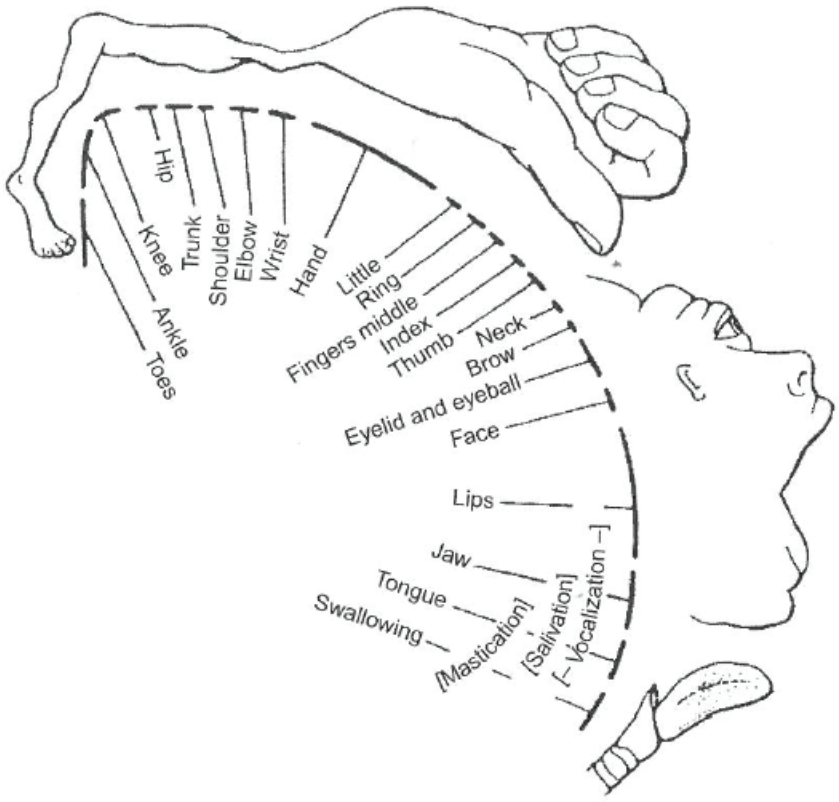

Figure 2. 'Homunculus'. The motor map from Penfield and Rasmussen (1950). Adopted from motor cortex, by David Rosenblum, in Human motor control (second edition), page 70. Copyright © 2010 Elsevier Inc.

Beyond the description in the manuscript of Penfield's, the somatotopy in M1 is interpreted to be an sequentially ordered, point-to-point map, within which different body parts, ranging from face to lower limb, are progressively arranged from the medial to lateral portion of the precentral lobe.

However, in both primate and human, accumulating evidence from stimulation, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) researches, challenges this simplified organization of simple movements in M1 (Sanes and Schieber, 2001; Schieber, 2001) in two aspects, the overlapped representations between body parts, and the less sequentially ordered representation within small body part, i.e. hand region.

In primate, intra-cortical micro-stimulation (ICMS) is used to excite the motor cortex with optimized precision. In the study of Stepniewska (Stepniewska et al., 1993), researchers aim to

explore not only the representation of different body parts in M1, but also its connection with non-primary motor cortex. Their result mirrors the general organization in human motor cortex, with face representation occupies the most ventral part of M1, tail and hindlimb lie on the most dorsal part, and the forelimb is represented in-between **(Figure 3)**. Interestingly, in this study, two subregions are identified at rostral-caudal level in M1, which are a caudal region with larger pyramidal cells and a rostral M1. This local anatomical uniform in M1 is also reflected on distinct ipsilateral connections: caudal M1 is primarily connected with somatosensory areas while as rostral M1 is connected with non-primary motor regions and somatosensory cortex. Therefore, the functional organization in Penfield's map is somehow too simplified which doesn't reflect the difference in somatotopy with respect to distinct functional subregions.

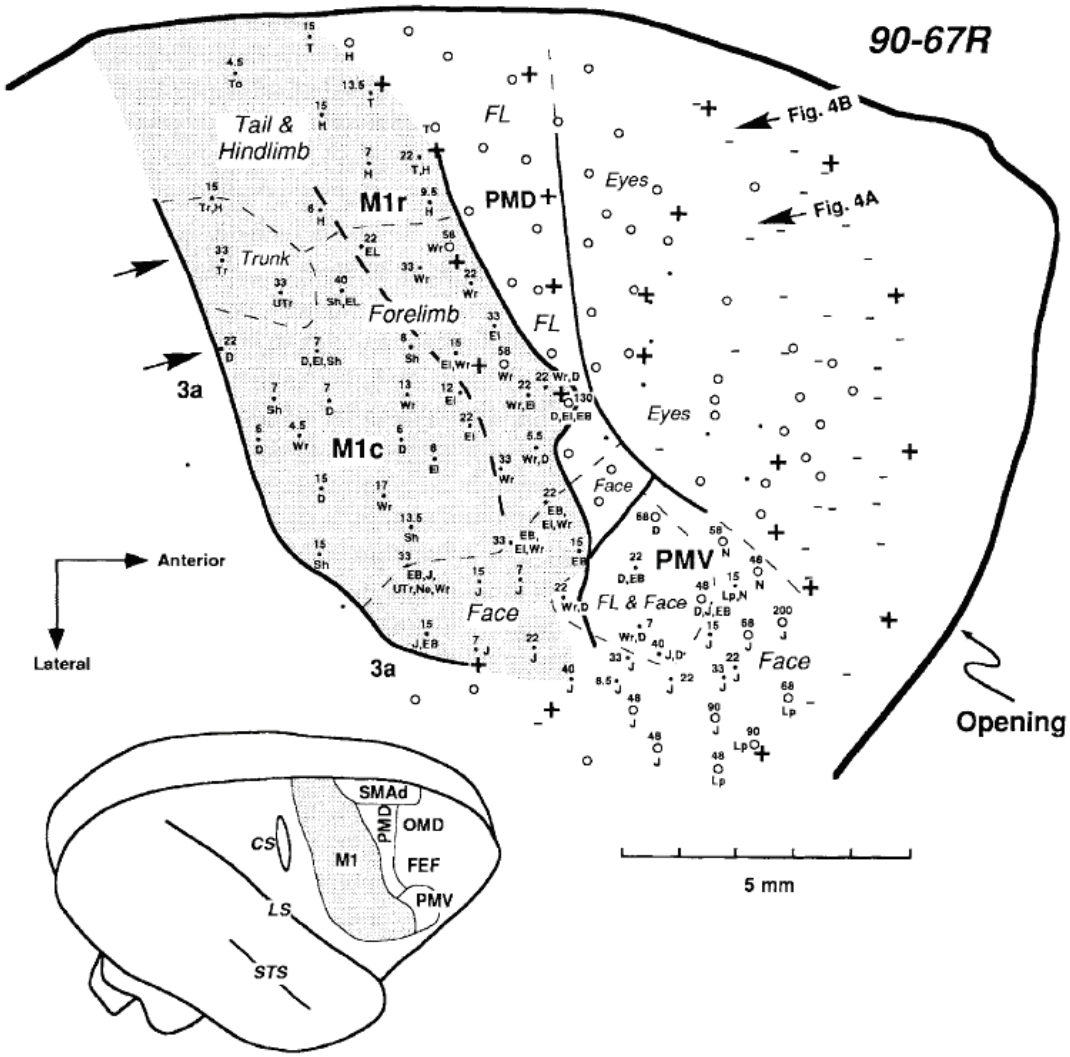

Figure 3. The stimulation sites on the architectonic map of the right frontal cortex of one owl monkey. From the study of Stepniewska (1993).

At the same time, PET (Corbetta et al., 1993) and fMRI (Ogawa et al., 1990) studies aim to explore the functional organization of voluntary movements in human sensorimotor cortex, with larger sample size than primate and patient studies. Most of these studies have special focus on the representations between limbs, i.e. hand vs. mouth, hand vs. elbow etc., or within-limb, i.e. fingers, wrist and elbow.

In the early 1990s, Grafton and colleagues did a series of studies in order to explore the functional organization of simple movement by imaging the cerebral blood flow (CBF) using PET scan. Studies of this kind interpret the changes of task-specific regional cerebral blood flow (rCBF) as the indicator to find the anatomical region specific to a certain motor or cognitive function. (Corbetta et al., 1993). At first, they recruit healthy subjects and guide them to perform motor tracking task with arm, finger, tongue and foot separately. rCBF is compared with control group in different task conditions and they discover some brain foci having reproducible relative increases of rCBF specific to certain movement condition (Grafton et al., 1991). The arrangement of these foci along the precentral lobe is similar with somatotopic organization of evoked movements of different body parts in Penfield's study.

Then, using the same motor tracking task and PET scan procedure, Grafton and colleagues further explore the somatotopy within-limb (Grafton et al., 1993). In this following study, movements of index finger, thumb, wrist, and elbow are executed independently, changes of relative CBF is measured in the contralateral M1 and SMA. Result indicated that the representation foci of shoulder, elbow, wrist and index finger and thumb arrange progressively in M1 at superior- inferior level **(Figure 4B)**. Also, despite the overlap between the representations of different movement conditions, they also report a significant difference in the locations of the peak activations at medial-lateral and superior-inferior levels, indicating independent functional localization between- and within- limbs.

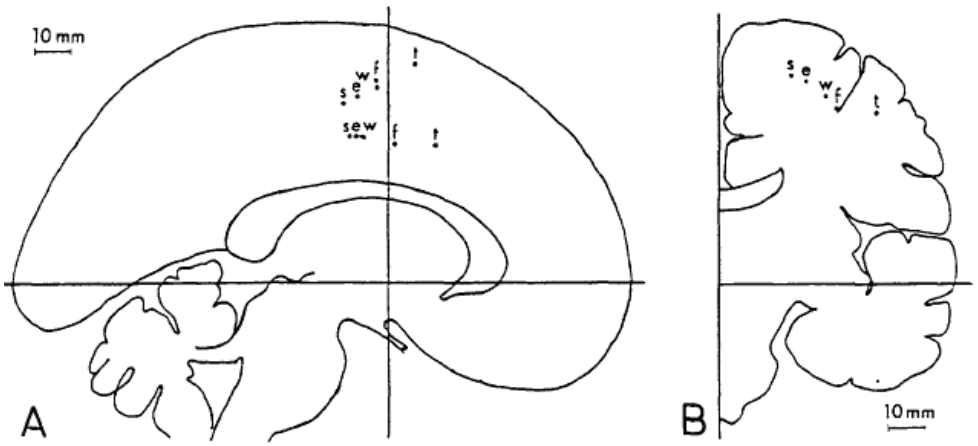

Figure 4. the location of peak relative CBF with movement of shoulder(s), elbow (e), wrist(w),index finger(f) and thumb(t). From the study by Grafton (Grafton et al., 1993, Figure1)

The fMRI technique with better spatial resolution than PET is also used to identify the functional localization of voluntary simple movements of healthy human subjects. Rao and colleagues map the voluntary movements of hand, arm and foot of healthy subjects, and their result confirms that fMRI is capable of displaying the general somatotopic organization in M1 in individual subject (Rao et al., 1995).

Later, with the progress of data analysis methods, in the 2000s, a series of fMRI studies take advantage of high-resolution MRI and aim to study the somatotopy in M1. Some studies pay attention on the existence of within-limb somatotopy. Indovina and colleagues (Indovina and Sanes, 2001) examine the within-limb functional localization by calculating the geographic center of clusters that are specific to simple digit movements, including the movements of thumb, index and middle finger. In this experiment, subjects are guided to perform flexion/extension of each digit independently. Researchers report statistical separable geographic center for each movement in motor cortex; however, the statistical power for the homunculus pattern is weak. That is to say, the relative larger representation of thumb, which is obvious in Penfield's map, is not exhibited in this fMRI study.

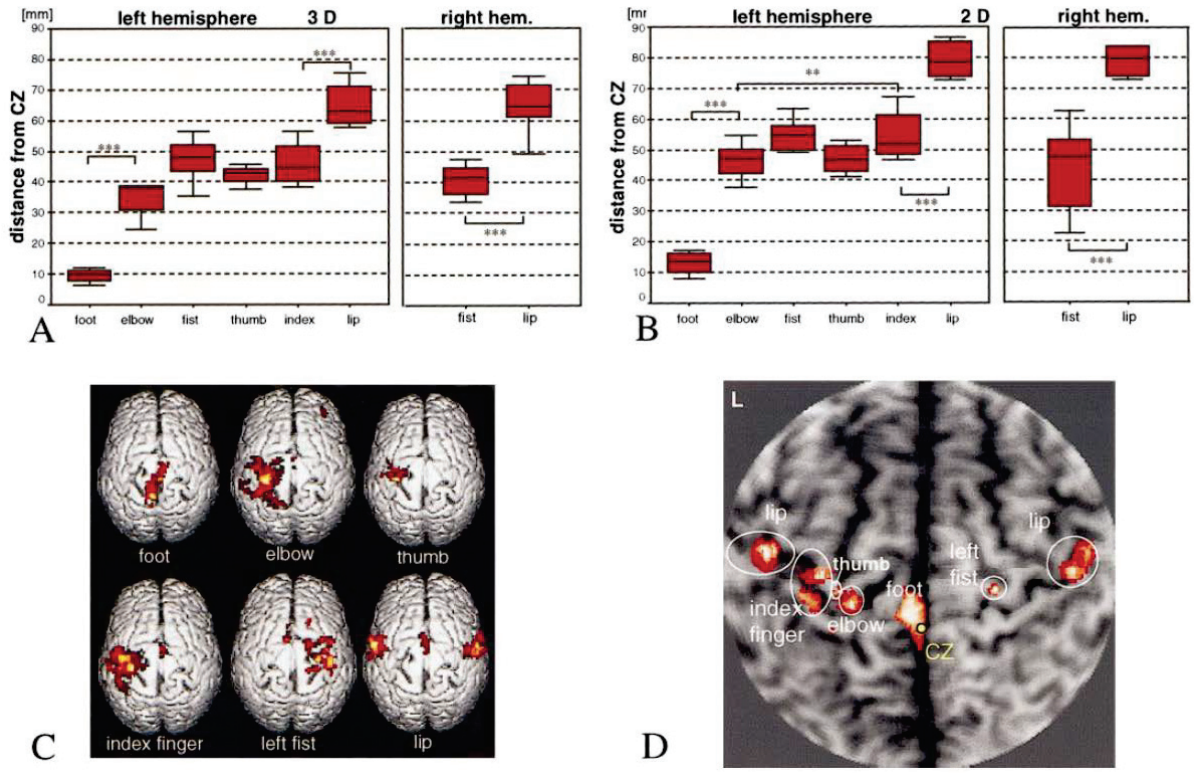

Figure 5. An example of the result from fMRI study (Lotze et al., 2000). Activation volumes of within-limb movements occupy brain regions with relative overlapping (C, see elbow, thumb and index finger).

However, the results from fMRI studies also exhibit an complicated issue on the functional organization in sensorimotor cortex, which is the overlapping of representations between activation volumes, especially for within-limb movements (Beisteiner et al., 2001; Hluštík et al., 2001; Indovina and Sanes, 2001; Lotze et al., 2000; Rao et al., 1995) **(Figure 5)**. This kind of overlapping could also be seen in PET study, where rCBF specific to one movement type also overlaps with another (Grafton et al., 1993). In fact, if we read the report of stimulation study in both primate and human carefully, the stimulation sites almost all intermingle **(Figure 1 for human M1, Figure 3 for monkey M1)**. Particularly, due to the advantage of human study in probing the sensory representation in cerebral cortex, it is obvious that not only the movement sites but also the sensation sites interleave between adjacent body parts (Penfield and Boldrey, 1937) (Figure 1).

Extreme caution should be taken when we extract information and interpret the result of Penfield's work. In his original study, Penfield doesn't propose a map with sharp border between body parts, in contrary, he emphasizes in his manuscript that 'movement appears at more than one joint simultaneously when stimulation was applied'. Apparently, distributing and also overlapping maps of functional localization already exist ever since the discovery of 'homunculus'.

Does an orderly somatotopy of simple body movement exist in motor cortex? How can we couple the both distributing and overlapping neural responses observed in MRI studies? These questions seem to be beyond the capability of imaging study in human. In fact, under these doubts, we ask a more fundamental question: in fMRI study, what does the neural response of simple movement represent on earth? Is it the basic functional unit with respect to movement? In fact, as has been shown early in the recording study by Kakei and colleagues, in M1, both neurons displaying muscle-like activities and neurons displaying movement-related activities can be found (Kakei et al., 1999). Thus, M1 is considered to involve in the process of not only low-level parameter like muscle force, but also the absolute direction of the movement.

By far, two distinct theories concerning the motor unit in M1 exist. One hypothesis is that single muscle is innervated by motor cortex in terms of small 'cortical efferent zones', which indicate separate and distributing region in the motor cortex sending motor command to a single motoneuron pool (Asanuma and Rosén, 1972a, 1972b); this hypothesis is made mostly based on the result from stimulation studies. The other hypothesis (Andersen et al., 1975) claims that each colony of cortical efferent zones distributing in motor cortex innervates one single motoneuron pool, and this cortical colony is called 'motor synergy'. Recently, ICMS and histological studies come up with accumulating evidence to support the later view.

I.1.2 Motor synergy in motor cortex: synergetic organization of muscular control

Synergetic control of muscle group is not a new assumption in motor control theory, it is adapted to address the degrees of freedom issue in human motor control (Bernstein, 1967). The hypothesis is that functional linkage between different motor units reduces the degrees of freedom when an action is called up. This structure of functional organization underlies synergetic motor control.

On the spinal cord level in vertebrate, microstimulation has been used to identify the map of behavior repertoires, (Bizzi et al., 1991)(Giszter et al., 1993) (Tresch et al., 1999)(Lemay and Grill, 2004). In studies of this kind, researchers found that when stimulating on one foci of spinal cord, discrete and specific muscular output could be decomposed into an invariant group of force filed. Interestingly, when two stimulations are applied at two sites simultaneously, the pattern of force field could be explained by the linear summation of the force field generated from each of those sites independently (Mussa-Ivaldi et al., 1994). These observations support the hypothesis that, at the spinal cord level, a discrete group of muscles that is called muscular synergy could the basic unit pf motor apparatus innervated by the motor command from spinal cord.

While on the level of cerebral cortex, motor synergy is also identified in the motor cortex of primate and human. Electrical stimulation on sensory and motor cortex always evokes some multi-joint movements (Penfield and Boldrey, 1937) (Stepniewska et al., 2005) (Graziano et al., 2002) (Haiss and Schwarz, 2005; Ramanathan et al., 2006), the relevance of these passively evoked actions with those naturalistic actions is examined. For the first time, Graziano and colleagues apply electrical stimulations lasting for 500ms on different sites distributing on the motor cortex of primates (Graziano et al., 2002). According to their rationale, the long-duration stimulations are more physiologically realistic than those brief ones. With electrical stimulation of this kind, they manage to evoke some intriguing actions in behaving monkeys. An example is shown in the figure 6G, when electrical stimulation is applied on a specific site, monkey always adopts a mouth/tongue posture that is similar with its ‘apple-eating’ posture in natural condition, no matter the initial position of its mouth and tongue before the electrical stimulation is applied. This final posture effect is also found on other sites of motor cortex where monkey’s forelimb movement can be evoked (Figure6 A-F).

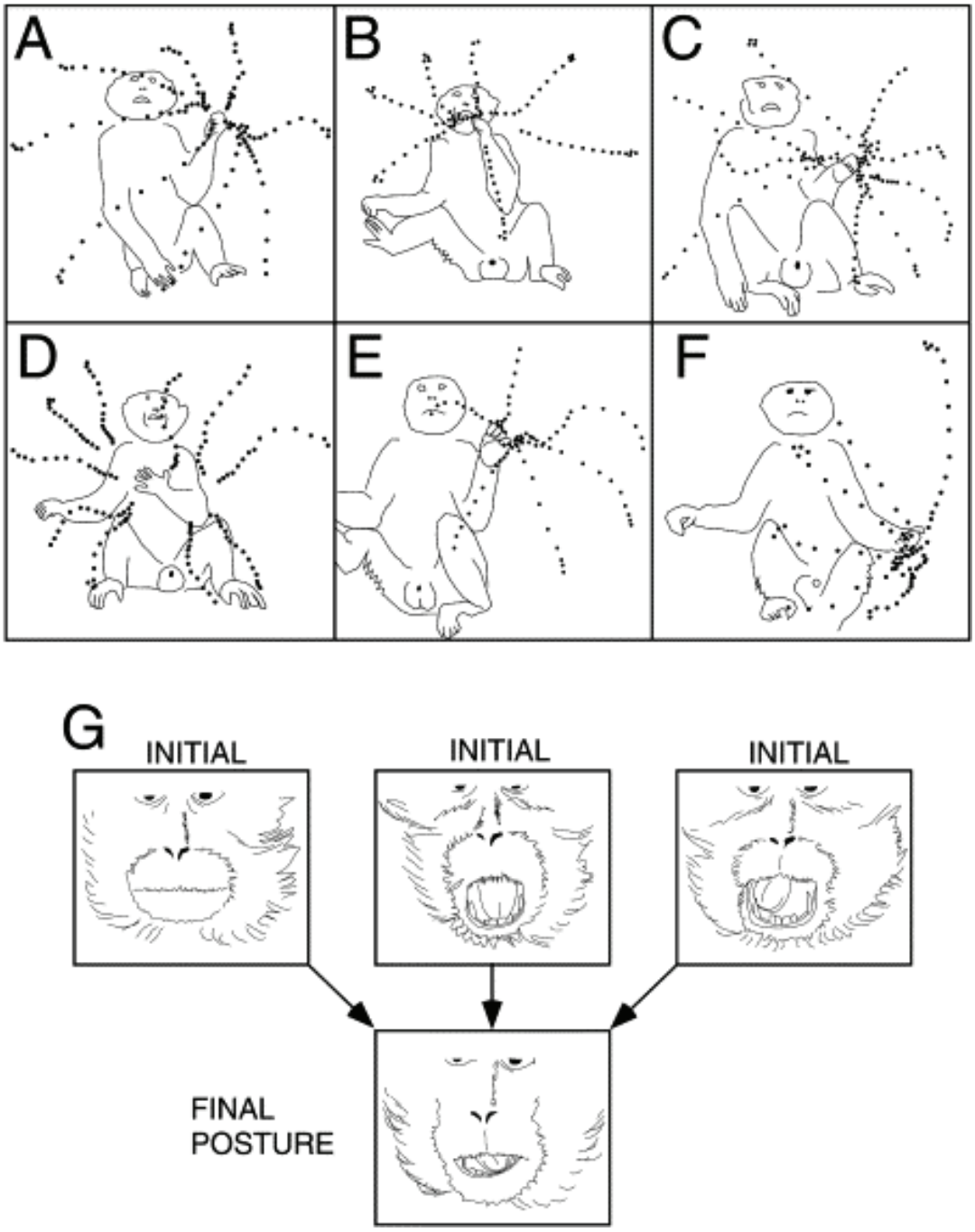

Figure 6. Six characteristic postures evoked when stimulate different sites in motor cortex of monkey (A-F). Black dots indicate the pathways of movements; they all lead to a final posture for one specific stimulation site. G. One example of the final mouth/tongue posture when stimulation is applied on one site in motor cortex of monkey, no matter the initial position of its mouth and tongue. (Graziano et al., 2002).

In a following-up study, Aflalo and Graziano further explore the neuronal mechanism underlying these effects (Aflalo and Graziano, 2007). They analyze the activity of single-neuron in relation with several main models tuning to movements, such as hand speed, hand direction, final posture of hand and final multi-joint posture of arm. The result indicates that among these models, the final multi-joint posture of arm accounts for most of the neuronal variance (36%) compared to other models (8%-22%), which implies that neurons in motor cortex codes predominantly the final posture of movement. The authors also argue that this character of motor neuron is of ethological meaning for daily life, because it is important to maintain a stable posture and make focal adjustment of movement parameters when perform a motor task.

Recently, motor synergy is also found in human motor cortex. In the study by Desmurget and colleagues, when direct electrical stimulation (DES) is delivered to some sites distributing along the precentral gyrus (PrG), action such as closing hand and moving towards opening mouth could be evoked (see figure 7C, right panel) (Desmurget et al., 2014). The stimulation site of this kind is called hand/mouth motor synergy by the authors. In this study, hand/mouth motor synergy could be found in both child and adult (see figure 7A).

Throughout its history, DES has been frequently criticized to be not appropriate in exploring cognitive functions of the brain (Strick, 2002)(Borchers et al., 2012), especially when intriguing effects such as ethological actions (Graziano and Aflalo, 2007) and conscious motor intention (Desmurget et al., 2009) are triggered, and have never been observed with traditional method. Most of those arguments concentrate on the mechanism underlying electrical stimulation, such as the artificial effect caused by current spreading.

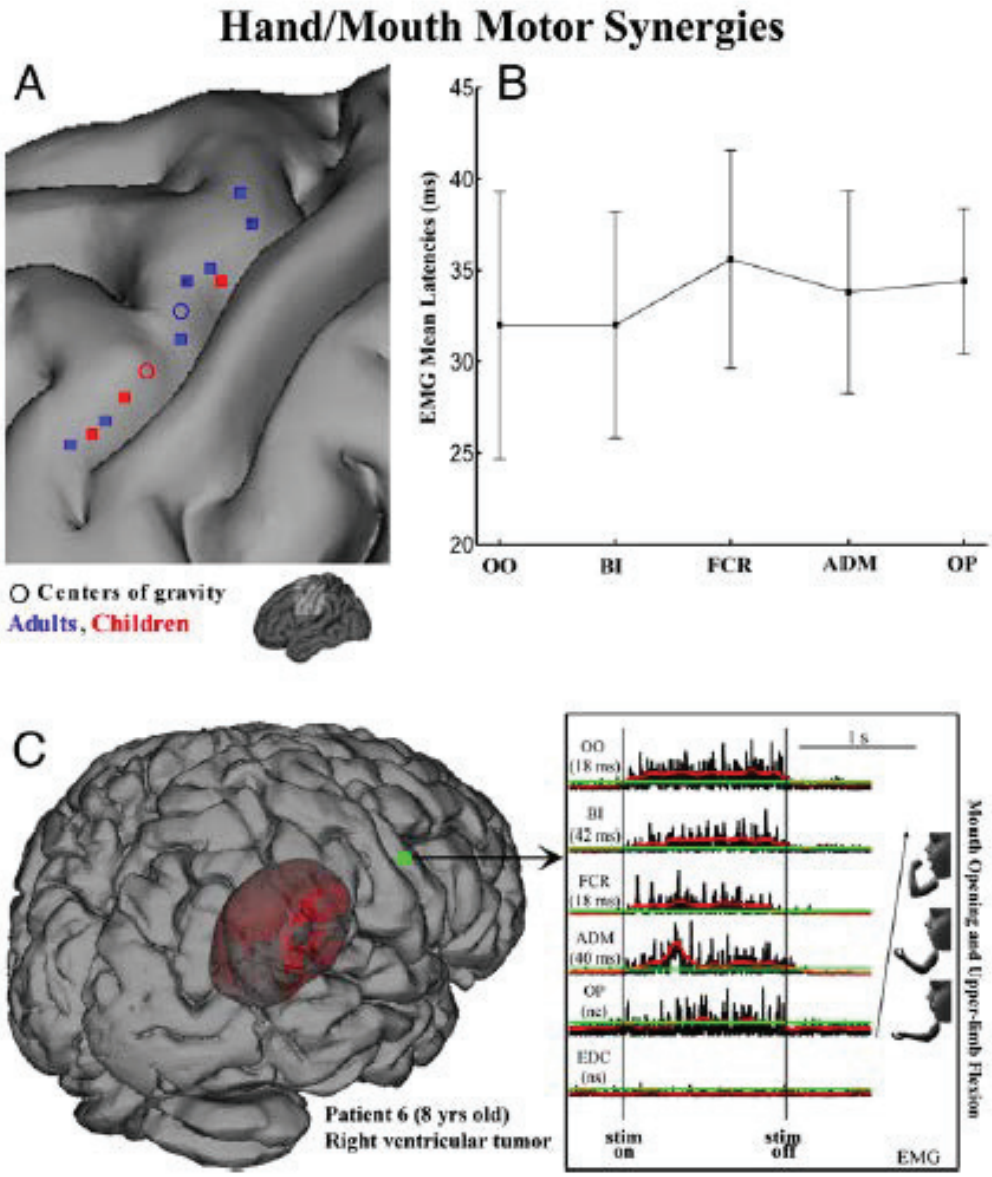

Figure 7. Hand/mouth motor synergy in precentral gyrus (Desmurget et al., 2014). Cortical stimulation sites of hand/mouth motor synergies distributing on PrG of adults and children(A) . mean EMG latencies recorded from muscles involved in hand/mouth action (B). one case example of a 8 year-old participant (patient), the stimulation site in PrG and the evoked EMG form of related muscles(C).

Muscle synergy is proposed as the unit of the musculoskeletal apparatus that is innervated by CNS to simplify the motor control. According to this concept, it is the synchronous and invariant activation pattern of a group of muscles. Overduin and colleagues systemically study the muscle synergy recruitment in grasping behavior of primate, and they are able to identify a limited number of muscle synergies that could account for most of the variation in muscle activity across two rhesus monkeys and different task variables depending the size and shape of objects to grasp (Overduin et al., 2008).

Following this finding, they further explore the physiological basis of muscle synergy in primate (Overduin et al., 2012). By delivering long-duration, ICMS to different sites on motor cortex (Figure 8), they evoke postural movements similar to those evoke by Graziano (Graziano et al., 2002). A comparison of the muscle activations between ICMS-evoked and naturalistic postural movements (Figure 9 A) reveal very high similarity between the two, in both the numbers of decomposed muscle synergy (Figure 9 B and C) and the pattern of these motor synergies (Figure 9 D). This is consistent with the finding by Graziano, in which they also confirmed some common character between the spontaneous behavior and the stimulation-evoked postural movements of primate (Graziano et al., 2003). These limited and small number of decomposed motor synergies, on which stimulation could evoke naturalistic like postures, distribute in the motor cortex and premotor region.

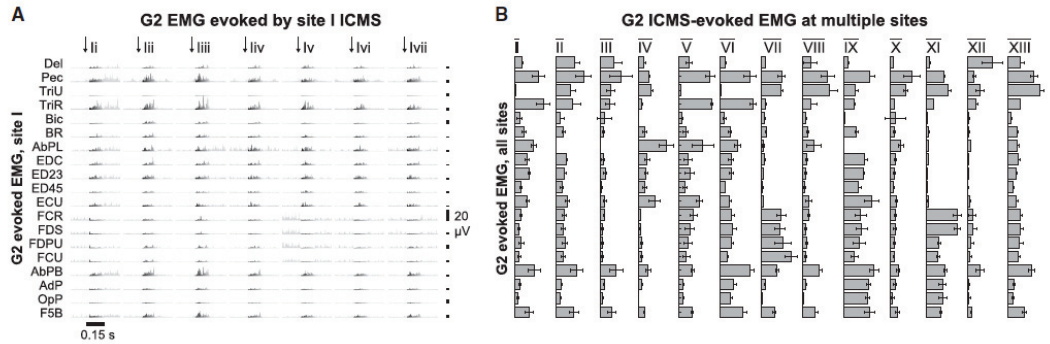

Figure 8. **Electromyograms of ICMS-evoked muscle activation** (Overduin et al., 2012)**.** Muscles(vertical axis) activations recorded from one stimulation site on the motor cortex of one rhesus monkey (A). Mean (gray bar) and SD of muscles activations of all 13 stimulation sites in one monkey.

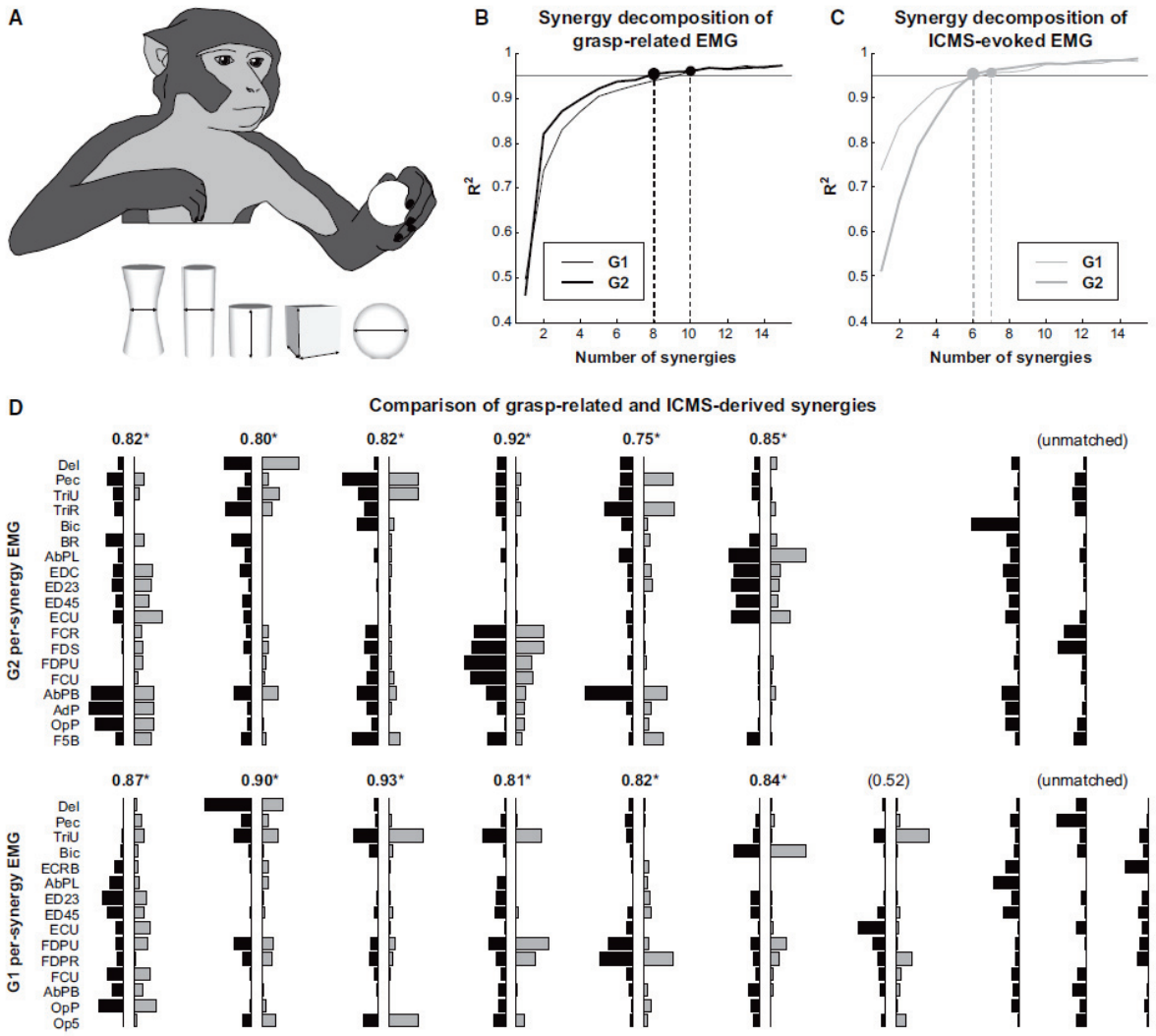

Figure 9. Comparison of muscle activation patterns between ICMS-evoked and naturalistic movements of monkey (Overduin et al., 2012).

Recently, computational algorithms(Avella et al., 2003) (Ting and Macpherson, 2005; Torres-Oviedo et al., 2006), such as non-negative matrix factorization algorithm (NMF), independent factor analysis and independent component analysis, are adapted to identify the

pattern of muscle synergies based on complex electromyography (EMG) data that are obtained during natural movements.

In human, this kind of computational analysis also provides rich results. In a study by Torres-Oviedo and colleagues, healthy human subjects are guided to make postural responses involving the movements of ankle and hip, meanwhile, EMG of related muscle activations are recorded (Torres-Oviedo and Ting, 2007). Researchers find that very few numbers of muscle synergies could be decomposed with specific computational method to account for variation of muscle activation patterns. Similar analysis are also used to exam the vulnerability of muscle synergy after cortical brain lesion caused by unilateral stroke (Cheung et al., 2009). Very interestingly, muscular synergies extracted from the EMG data of affected- and unaffected arms don't demonstrate much differences despite the impairment on motor performance. This result support the view that muscle synergy is specified in the lower level of motor system, possibly in spinal cord or brainstems. Indeed, electrophysiological experiments confirm that the neuronal activity in spinal cord is related to the activation of muscular synergies but not single muscle (Hart and Giszter, 2010). Under such cases, motor cortex that sends descending signal to the interneurons or motor neurons might play a role in selecting and/or activating the muscle synergies specified in lower level. How does the interruption of descending motor signals effect the selecting of muscle synergies? The same group further explores this question with respect to the severity of functional impairment and the stroke onset time. Apparently, basic independent muscle synergies are not all preserved in severely impaired patients (Cheung et al., 2012).

Indeed, the factorization of postural movements, evoked by stimulation or spontaneously executed, into limited muscle synergies facilitates our understanding of functional organization of sensorimotor system, for example, by combining this method with stimulation studies (Overduin et al., 2008, 2012) and lesion studies(Cheung et al., 2012). However, the somatotopy of simple movements of different body parts, which we consistently observe in motor cortex since Penfield, has not been well merged with the concept of motor synergy (Desmurget et al., 2014).

One motor neuron and the muscle fibers it innervates are called a motor unit (Rosenbaum, 2009). In a delicate design, subjects are trained to single out motor units, for example, the control of abductors pollicis abbrevis independently(Basmajian, 1963). However, even simple

finger movement requires the control by multiple motor unit (Lang and Schieber, 2004; Reilly and Schieber, 2003) . On one hand, physiological examination in primate could uncover direct innervation relationship between cortical neurons and motoneurons, but fail to explain the data in the larger scope such as simple movement; on the other hand, DES with restricted effect on small cortical sites provide the map of simple movements(Penfield and Boldrey, 1937) and postural movements (Desmurget et al., 2014) but demands tremendous amount of data and tests to obtain a full description involving all body parts. All methods display a common feature that is the overlap between functional representations of different motor units or different body parts. Under such circumstance, some efforts are made to keep digging the fMRI data (Cunningham et al., 2013; Meier et al., 2008), and researchers start to try to figure out the mechanism underlying the volume overlap of activations. Thus, further study is in need to reveal the physiological basis of activation volume of different simple movements and the overlapping patterns.

As human, we have dexterous finger movement that is the key for using tools. Many researches have investigated the musculoskeletal mechanism (Lang and Schieber, 2004; Reilly and Schieber, 2003; Schieber, 1995) , the kinematic and dynamic control by CNS (Beisteiner et al., 2001; Olman et al., 2012; Shibasaki et al., 1993). However, there are inevitable constraints when exploring the neural basis of so-called independent finger movements, due to the passive mechanical coupling of neighboring fingers, the multi-tendons control by extrinsic muscles, etc.

In retrospect of previous fMRI studies, evidence is in favor of the existence of independent representation and somatotopic organization of large body parts in motor cortex, despite the complicated results of peak activation, geographic center and activation volumes (figure 10) (Indovina and Sanes, 2001) , across study and task design (Sanes and Schieber, 2001) (Olman et al., 2012). Also, researchers have reached a consensus that the selective representations of simple finger movements are not orderly organized but overlap extensively. Thus, alternatively, future fMRI studies should focus on the organization pattern of activation volumes, within hand region and within-limb. Together with the independent peak activation or geographic center, overlap activation volumes of simple finger movements could provide more information of the neural basis of M1 functional organization.

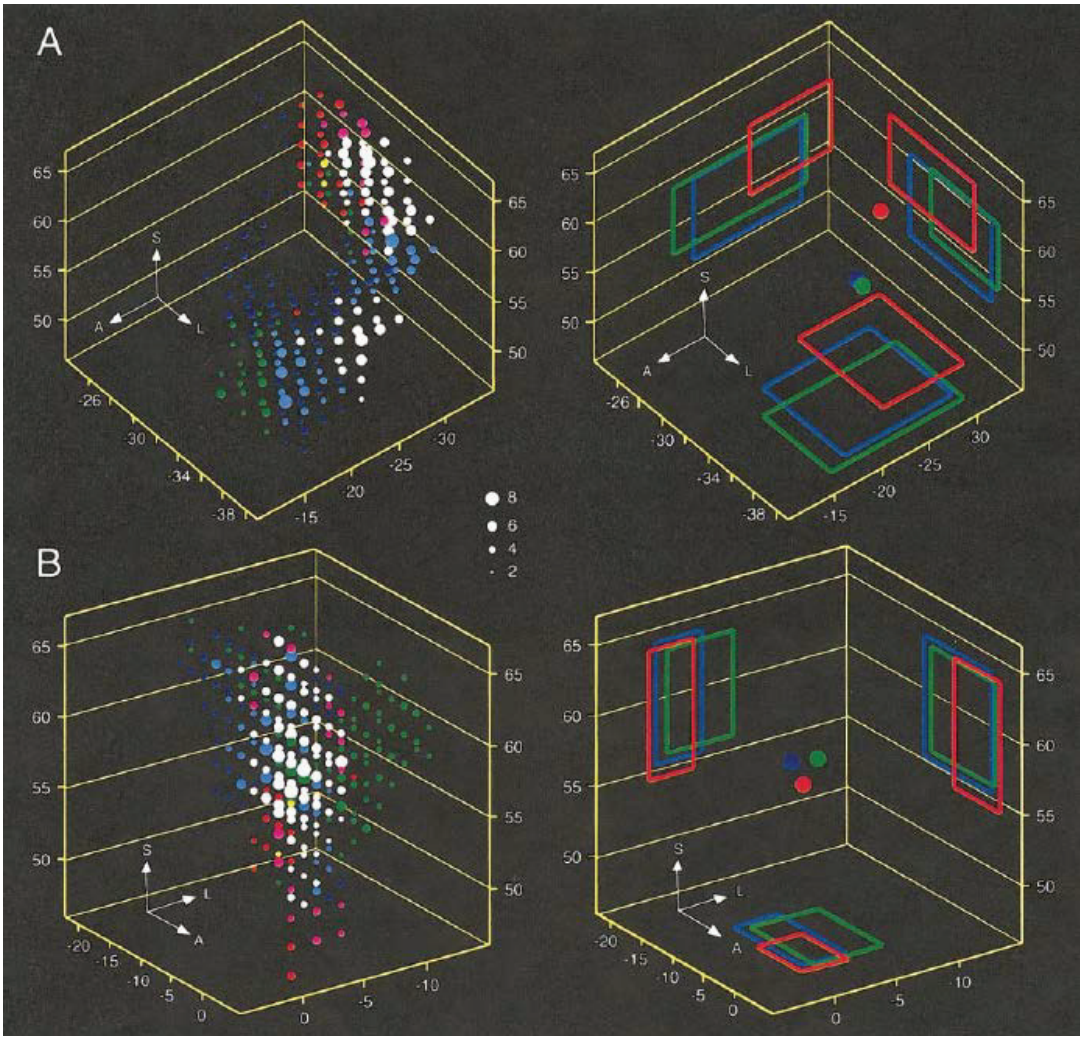

Figure 10. **Geographic centers of simple flexion/extension movements of independent fingers in M1 (A) and SMA (B)**(Indovina and Sanes, 2001) . Blue, green and red dots represent first to third finger.

I.1.3 Two anatomical subdivisions in M1

Some other features of the functional organization in M1 are also discovered. As we have discussed above that the M1 of primate is not an uniformed brain region (Stepniewska et al., 1993) (Matelli et al., 2004). It contains two subregions with distinct cytoarchitectonic features and connectivity pattern. Similarly, in human, area 4 can be subdivided into an anterior(4a) and a posterior (4p) part also based on quantitative cytoarchitecture differences (Geyer et al., 1996). In this study, using PET scan, researchers revealed representations of fingers in 4a and 4p separately. A following-up study further examine the modulation by attention in 4a and 4p during right index finger movement(Binkofski et al., 2002). The task is to move right index finger to draw a well-shaped 'U' at constant amplitude and speed, thus requires certain level of attention to this action. Result indicates that only area 4p is effected by the modulation of attention to action thus these two subdivisions of M1 contributes differently to skilled movement.

Recently, probabilistic cytoarchitectonic map has been widely used in functional imaging study (Eickhoff et al., 2005, 2006a, 2007a). Assignment of functional activation to anatomical atlas with subdivisions that could better couple with the functional complexity is in need. To this end, in our fMRI experiment, the functional organization in M1 of simple movements is re-examined with respect to the subdivision based on the probabilistic cytoarchitectonic map obtained with quantitative analysis of cytoarchitecture in human (Amunts et al., 2007).

I.2 Posterior parietal cortex in action

The posterior parietal cortex (PPC) is considered part of the motor system (Rizzolatti et al., 1997)(Fogassi and Luppino, 2005). Its involvement in sensory and motor processing has been investigated mainly in three aspects, including sensory-motor integration (Andersen et al., 1997; Colby and Duhamel, 1991; Rizzolatti et al., 1997)(Andersen and Buneo, 2002), action organization (Fogassi and Luppino, 2005), as well as action understanding (Rizzolatti and Craighero, 2004).

The human parietal cortex locates between frontal and occipital lobes. On the lateral surface, it is separated from frontal lobe by the central sulcus, but there is no clear macro-anatomical separation of it from occipital and temporal lobe. On the medial surface, it could be distinct from occipital lobe by the occipital-parietal sulcus, and from the cingulate gyrus by the sub-parietal sulcus. Also, on the lateral surface, the intraparietal (IPS) that contains an oblique and a horizontal portion grossly divides the parietal cortex into the superior parietal cortex (SPL) and the inferior parietal cortex (IPL).

Three major schools propose their cytoarchitectonic maps that subdivide human parietal cortex in different ways. Brodmann brings up the most adopted one in 1909 **(Figure 11A)**, which distinguishes parietal cortex into four subregions, namely area 5 and 7 in the SPL, as well as area 40 and 39 that constitute IPL. A second influential map is made by von Economo and Koskinas in 1925(**Figure 11 B**), in which parietal cortex is divided anterior-posteriorly into PDE, PEm, PEp, PEg, PFt, PFop, PFcm, and PG. However, the lateral bank of IPS, although on which variant involvements in cognitive tasks have been discovered in both behaving animal and human, is not well described in neither of the two maps. Thus, a detailed subdivision of IPS is also in need to explain its functional complexity.

A third school provides more completed parcellation based on cyto- and myelo-architectures, one of the most recent is the work by Caspers and his colleagues, they normalize their map into MNI space (Caspers et al., 2006)(Choi et al., 2006). They identifie six subregions at the anterior-posterior level, which are PFop, PFt, PF, PFm, PFcm, PFa and PFp (Caspers et al., 2006) (**Figure 11 C**), and in IPS, two subregions are also identified by the same team, which are hIP1 and hIP2 (Choi et al., 2006).

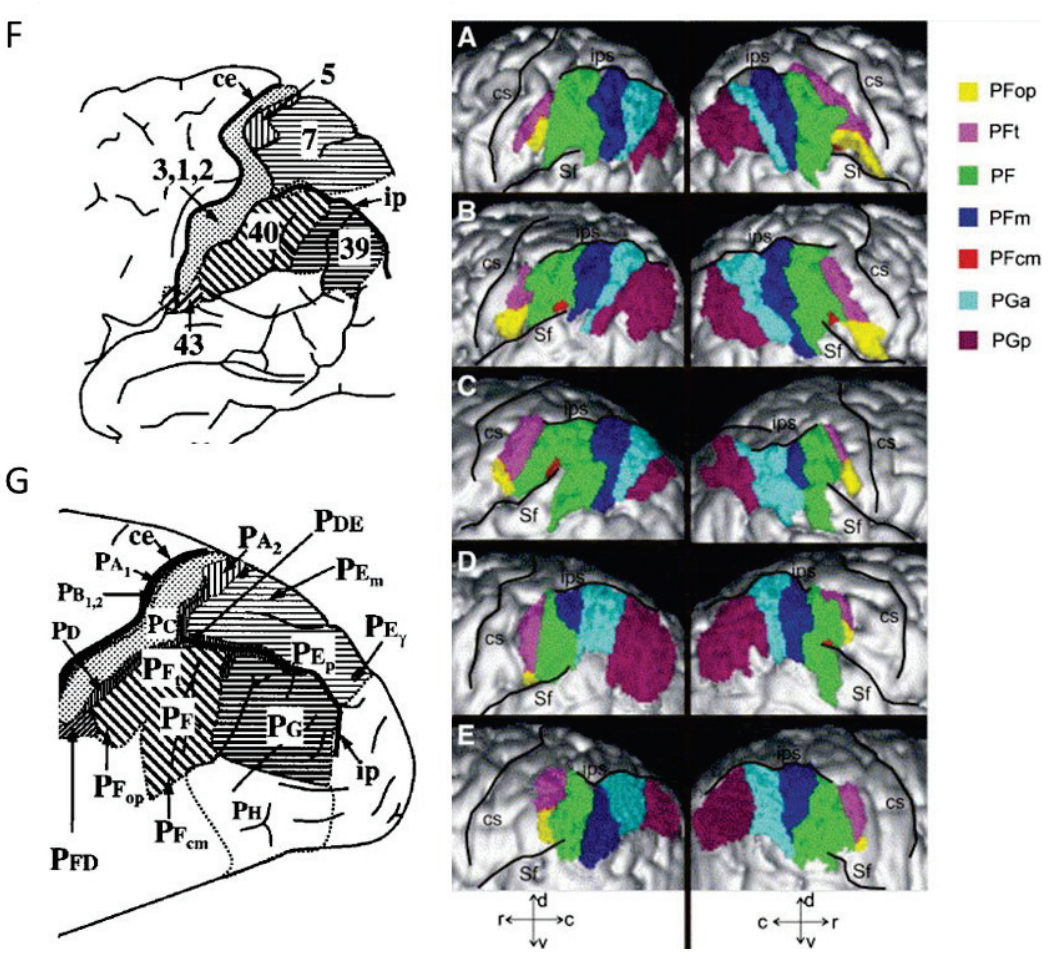

Figure 11. **Architectonic subdivisions of human parietal cortex**, by Brodmann(1909) (F), von Economo and Koskinas (1925) (G) (adapted from Zilles in 2001) and Caspers et.al (2006) (A-E).

In primate, the IPL comprises the gyri surface, the lateral bank of the IPS, the anterior bank of the caudal third of the superior temporal sulcus (STS), and a small portion of the medial wall. Based on cytoarchitectonic characters, it is defined as one single region by Brodmann (1905) as area 7. Vogt and Vogt (1919) further divide it into two subregions, a caudal-medial part 7a and a rostral-lateral part 7b. Later, adopting the nomenclature of von Economo and Koskinas (1925), von Bonin & Bailey (1947) confirm the existence of two subregions, which are a rostral portion PF and a caudal portion PG. However, these relative simple distinctions could not account for the intricate afferent and efferent connections with IPL. In the study of Pandya and Seltzer (Pandya and Seltzer, 1982), they explore the anatomical complexity of IPL in rhesus monkey by examining its architectonics and intrinsic connection pattern the same time. Based on distinct connectivity signatures, they are able to distinguish four subregions on the lateral convexity of IPL at rostral-caudal levels, which are PF, PFG, PG and Opt. This map is close to the result of a recent work by Gregoriou and colleagues, who combined the examination of the cytoarchitecture and myeloarchitecture of IPL convexity in 17 macaque monkeys (Gregoriou et al., 2006). In the map of Gregoriou, at rostral-caudal levels, the convexity of IPL is divided into PF, PFG, PG and Opt progressively from the most rostral portion to the most caudal portion.

Do these anatomical distinctions correspond to functional complexity found in PPC? Single neuron in area 7 of behaving monkey displays both sensory and motor properties (Mountcastle et al., 1975) (Andersen et al., 1987). Also, neurons in parietal cortex discharge differently in distinct locations and tasks (Hyvärinen and Shelepin, 1979) (Lynch et al., 1977) (Robinson et al., 1978). Thus it is considered having higher-cognitive function such as sensory-motor integration.

From recording studies in primate, so far it is well known that the neuronal response in the caudal portion of IPL is mostly visual and visuomotor, whiles in the rostral portion it is more somatosensory and somatomotor. In an early neurophysiological study, Hyvärinen and colleagues confirm the functional distinction of two cytoarchitectonic subregions in IPL by Bonin & Bailey (Hyvärinen, 1981). They systematically investigate the functional organization of IPL by presenting visual, somatomotor or somatosensory stimuli to awaking macaque monkeys. According to their results, in general, visual and oculomotor responses occurred in PG(7a), somatosensory responses concentrated mostly in PF(7b).What's more, somatomotor responses distribute across area 7 in somatotopic manner, such as that the activities of mouth and hand actions could be found in a rostral portion of PF(7b), whileas the activities of eye movements occur in the PG (7a) regions. Recently, another neurophysiolocal study further examine the effects of visual, cutaneous and motor stimuli on the convexity of IPL in relation with the recent subdivision by Gregoriou (Gregoriou et al., 2006) (Rozzi et al., 2008). In this study, Rozzi and colleagues train monkeys to perform naturalistic actions related to objects, such as biting, hand-mouth grasping, grasping, bringing to mouth, reaching-grasping, reaching etc.. Similar with the findings of Hyvärinen, they find motor responses distributing across the convexity of IPL, visual and oculomotor responses mostly concentrating in PG region and somatosensory responses mostly occurring in PF region. What's more, the motor responses distributing in IPL has a somatotopic organization, such as that actions related to mouth mostly activating the PF region, actions related to hand distributing across PFG and PG regions but most concentrating in PFG region, actions related to arm exciting more the PG region. That is to say, distinct functional organizations with respect to different stimulation modalities are found in different anatomical subdivisions, with relative overlap.

In primate, IPL is widely connected with brain regions of multiple sensory modality and of higher cognitive function. For example, the rostral most region, area PF, has afferent connection with the ventral part of post central gyrus (Brodmann area 2)(Pandya and Seltzer, 1982), the extrastriate parietal-occipital sulcus (POa) receives rich inputs from visual cortex V1, V2, V3 and MT, and has connection with several IPS subregions (Pandya and Seltzer, 1982)(Colby et al., 1988), meanwhile, the subregions of IPL convexity also send distinct output connections to the frontal lobe (Petrides and Pandya, 1984), including frontal motor areas. The PF region is the most anterior portion projects mainly to the ventral part of area 6, the PFG and PG regions that are in the middle of IPL have major output connections with the ventral parts of area 46 and area 8, while the caudal part of PG region and the Opt region send projections mainly to the dorsal portions of area 46 and area 8, as well as the dorsal area 6 and area 24 in the cingulate cortex. Thus, the efferent and afferent connectivity of IPL as well as its intrinsic connections provide the neural basis of its role in visuo-motor control in the space.

Based on abovementioned anatomical and neurophysiological evidence, multiple theories exist regarding the role of IPL in behavior. Mountcastle et al. proposes that PPC is the *command center* issuing motor command in initiating motor behavior (Mountcastle et al., 1975) (Mountcastle, 1995). This theory of IPL is supported by the observation that neuronal activity preceding EMG activity could be recorded in IPL when monkeys perform oculomotor or hand movements (Mountcastle et al., 1975). However, many researches argue against this theory and propose that motor-related response is the efference copy of motor command organized in frontal lobe rather than motor command *per se*. An intuitive evidence is that although motor responses in area 7 are indeed preceding EMG activity, it is still slower than the motor responses recorded from M1, thus echoed with the hypothesis that motor-related response in IPL are likely the efference copy of motor command formed in frontal cortex.

Alternatively, another hypothesis is that IPL operates as a *sensorimotor interface*. As revealed by Andersen in 1980s, in primate, neurons of area 7 activate by both visual stimuli and oculomotor behavior (Andersen et al., 1987). Similarly, in human, lesion to IPL often interrupts both sensory and motor functions. Unilateral neglect of extrapersonal visual field is a symptom frequently observed in patients with right IPL lesion (Vallar and Perani, 1986). Patients exhibited selective difficulty in initiation and execution leftward movements towards targets in left visual

field (Mattingley et al., 1992, 1998). This observation demonstrates that the human IPL serves as an interface where visual information and directional motor command communicates to serve the behavior. Some studies focus on the integration of multimodal sensory information and transformation from perceptual coordinate to spatial coordinate needed to form early motor plan (Andersen and Buneo, 2002). The others are interested in the internal representation copied from motor command (Wolpert and Flanagan, 2001; Wolpert et al., 1995). Parietal lesion damages the internal mental representation and execution of movement (Sirigu et al., 1995), possibly because of its role in motor prediction. In the study by Sirigu et al. , patients with selective lesion in unilateral left or right PPC (area 7 and area 40, 39), and exhibiting impairment of hand movement execution, are guided to perform motor imagery task (Sirigu et al., 1996). Compared to normal control, these patients make incongruence estimations of their maximum speed in thumb-finger opposition task between imagery and actual movement conditions. Indeed, in primate, some parietal neurons predict the sensory changes before an eye movement by transiently shifting the receptive field (Duhamel et al., 1992), implicating the role of IPL in monitoring motor plan. In human, stimulation study also revealed the existence of abstract internal representations of movement in the IPL (Desmurget et al., 2009). In a pioneering study, DES delivered at IPL triggers motor intention without any movement being executed eventually. This abstract motor intention could be considered as an early plan of movement (Andersen and Buneo, 2002); and very interesting, in same subjects, stimulations on PM produces overt movements but without conscious awareness of doing so. Thus, the internal representation or motor intention in IPL is distinct from the motor command from frontal motor regions; also, since that the stimulation-triggered movements in PM bypass the IPL (Histed et al., 2009)(Desmurget et al., 2013), in which efference copy of motor command is processed, it is likely that conscious experience of motor intention is not related to motor preparation.

Although in primate, the anatomical complexity of IPL has been investigated relatively completely from many respects, such as cytoarchitecture, connectivity as well as myeloarchitecture, there are no clear homologies between the subdivision of IPL in primate and in human, which makes the inference from primate study even harder. Grossly, the subdivisions of IPL (PF and PG) by von Bonin & Bailey (1947) in primate are good homologues to those of von Economo and Koskinas (1925).

Despite the limitation of neurophysiological and DES studies, nowadays, the neuronal responses in human IPL during motor and cognitive tasks can only be noninvasively detected using fMRI and dedicated experiment design of mental chronometry. Besides, fMRI provides a better spatial resolution to localize functions to anatomical regions based on progressively well-defined atlas.

First, repetitive simple movements of different body parts, namely finger, elbow and ankle, have been found to have topographic representations on human IPL (Cunningham et al., 2013). In this study, researchers locate the geographic centers for each repetitive simple movement, and they found that the geographic centers of finger, elbow and ankle form two clusters separately within IPL. This structure of topographic map is quite different from that of somatomotor and somatosensory maps in M1 and S1, possibly implying different functional organization role in IPL.

Second, further studies focus on the representation of actions on IPL. Marc Jeannerod once proposes that mental motor imagery gives access to the internal representational stages of action (Jeannerod and Decety, 1995). To this end, neural response to in simulation conditions(Jeannerod, 2001), such as action observation and action imagery, as well execution of intended action are extensively examined in the past two decades. Buccino and colleagues studied the activations in PM and parietal cortex by asking participants to observe object-related and non-object-related action (Buccino et al., 2001), and they found that observation of mouth, arm/hand, and foot actions activated distinct foci in IPL, anterior IPS, and SPL. Later, in a recent study, Lorey and colleagues compare the action- and effector-specific maps on IPL, under action observation and motor imagery conditions separately (Lorey et al., 2014), and they find that during action-observation condition, action-specific maps are dominantly found in PPC, thus they argue that both action-specific and effector-specific maps exist in parietal cortex and the recruitment of certain map depends on several factors, including the forms of simulation (observation, imagery) etc.

Apparently, the topographic maps in terms of BOLD-signal changes depends on the task modality that is more complex than the motor-, sensory, cutaneous- related stimuli used in primate studies. Consequently, the nature of the neural responses manifest as BOLD-signal changes can not be easily attributed to sensory-related or efference copy of motor command,

because as has been indicated in primate, both could be recorded in parietal neurons. Under this circumstance, connectivity pattern could provide insight on this issue from another aspect. In primate, IPL has rich connections with visual cortex, frontal cortex as well as somatosensory cortex. Several groups investigated the functional and anatomical connectivity of parietal cortex in human. In a series of studies by Eickhoff and colleagues, they used probalistic tractography on diffusion tensor imaging (DTI) data, as well as functional connectivity analysis on fMRI data. Firstly, from histological defined distinct areas in parietal operculum(PO) that is considered as the secondary somatosensory cortex (SII) and comprises several subregions (Eickhoff et al., 2006b, 2006c), they found that anatomically and functionally, area PO1 is closer connected with the anterior IPL, IPS, thalamus and the opposite hemisphere, whileas PO4 has closer connectivity with postcentral gyrus , M1, PM and IPL(Eickhoff et al., 2010). These distinct connectivity patterns of IPL with SII and frontal motor regions could be the neural basis of the dinstinc functions of its subregions, for example, the anterior IPL.

However, the most recent subdivision in human IPL (Gregoriou et al., 2006) has not been well examined with corresponding functional complexity. Therefore, in this thesis, I investigated the representation map of simple movement in IPL, with special focus on the rostral part, including the PF regions defined by Gregorious's map. This region is likely the homology of monkey PF where complete somatosensory representation and motor responses of mouth, hand are both found (Hyvärinen, 1981)(Rozzi et al., 2008).

I.3 Motor intention and motor preparation

Accumulating evidence indicates that parietal cortex is related to motor intention. Researchers found that observation of others' action evoked neural responses in PM and parietal regions (Buccino et al., 2001). In primate, evidence indicates that neurons in IPL response differently to the goal of actions performed by the experimenter, for example, grasping action for eating or for placing evoked different motor responses of IPL neurons (Fogassi et al., 2005).

In human, the classic paradigm used to isolate conscious motor intention in cognitive task is 'Libet task'. Three decades ago, Benjamin Libet design a delicate psychophysiological experiment to measure the subject feeling of conscious intention (Libet et al., 1983). He asked subjects to voluntarily press a button at any time when they had an conscious intention to do so, and reported it according to clock presenting in front of them all through the experiment. Patients with selective lesion in parietal cortex has difficulty to report this conscious event (Sirigu et al., 2004), indicates the role of parietal cortex in generating conscious intention.

With Libet task, on average, subjects reported their motor intention approximately 200 ms in advance of movement onset. And very interesting, an electrophysiological marker could be detected as early as 1s before movement onset by Libet and other researchers using this paradigm (Haggard and Eimer, 1999; Sirigu et al., 2004). Thus, one may speculate the relation between this early unconscious neural activity and forthcoming conscious events. Contradict theories exist on the nature of the unconscious neural activity. the 'action then intention' view assumes that it reflects the preparation of upcoming button press movement (Haggard and Eimer, 1999; Hallett, 2007), therefore, conscious intention should be the consequence from this process. Alternatively, the 'intention then action' view assumes that unconscious neural activity doesn't reflect movement *per se* (Trevena and Miller, 2010), but the buildup to conscious intention and in turn triggers action (Fried et al., 2011).

In many studies using Libet paradigm, the motor task is simply press the button. Whileas the objective of these researches are usually more complex as to examine the causal relation of unconscious neural activity, conscious intention, and moor preparation. According to our knowledge of simple reactive movement, motor plan could be loaded in motor cortex during the stage of motor preparation before go cue; meanwhile. higher-order cognitive brain regions is

considered to exert proactive inhibitory control on the motor cortex to prevent overt movement before go cue. Similarly, when subjects are asked to perform voluntary index finger flexion, we assume that corresponding abstract motor plan could be also loaded when subjects placed the index finger on the button. It has been found that approximately 120ms before movement onset, the intermediate part of SMA triggers actual movement via release inhibition on M1 (Jaffard et al., 2008). Unfortunately, classic response task or go/no go task is not able to demonstrate the neural correlates of conscious intention because no demand of reporting this internal event. Based on the existing literature, it can be observed that RT/int and RT/ext are generally of similar magnitude (Desmurget and Sirigu, 2009; Desmurget et al., 2013). This temporal proximity could reflect the similarity in neural correlates of the two delays (Desmurget and Sirigu, 2012).

Therefore, despite this complexity, we designed a straightforward behavior experiment including simple reaction task and Libet task, in order to compare the cognitive process of motor intention and motor preparation.

Chapter II. Experimental contribution

II.1 Study 1- Somatotopy in human cortical motor system

1. Introduction

Somatotopy is the prominent feature of the functional organization in motor cortex. It has been examined using different techniques, such as electrical stimulation, PET, and fMRI, in primate and human. However, debate on the within limb somatotopy in M1 still exists. Previous fMRI studies showed extensively overlapping of activation volumes in motor cortex between pairs of single finger movements (Rao et al., 1995)(Beisteiner et al., 2001; Indovina and Sanes, 2001) **(Figure 10)**, while the coordinates of peak activation or the geographic center of the activations demonstrate separate representation of fingers. Despite this contradiction, there are two different theories concerning the functional organization in M1, one proposes that there is cortical efferent zones within which neurons that innervate a single motoneuron pool resides in a small zone in M1(Asanuma and Rosén, 1972a) , and the other theory claims that there are overlapped colonies of cortical efferent in M1, and within each colony, neurons innervates a single motoneuron pools concentrates (Andersen et al., 1975) .

According to the 'cortical efferent zone' view, we can make the hypothesis that if the activation volumes evoked by flexion/extension movement of single finger is related to the recruitment of a common 'cortical efferent zone', we should expect different level of overlapping between any two finger pairs. Thus, in this study, we will examine the somatotopy of single fingers in terms of geographic center and the overlapping pattern of their activation volumes.

Also, with recent findings in primate (Rizzolatti et al., 1997) and human (Culham and Valyear, 2006), IPL is also considered as part of the cortical motor system, however, its structure of the functional organization of simple movement is still not fully depicted(Cunningham et al., 2013). In primate, somatosensory and somatomotor organization have been discovered in relation the complex cytoarchitectonic subdivisions(Rozzi et al., 2008). And recently, an advanced subdivision of IPL based on architecture and connectivity is also proposed(Caspers et al., 2006), therefore, further study aiming to couple the anatomical and functional complexity of IPL is in need. In this experiment, we also studied the functional organization of simple movements in IPL, and we compared the location of its functional map with respect to this subdivision (Caspers et al., 2008).

2. Materials and methods

2.1 Subjects

Fifteen subjects (7 men, 8 women) participate in this study with written informed consent, experiment procedures are approved by the local ethical committee (CCPRB, Centre Léon Bérard, lyon). Subjects are all right-handed, with mean age of 23 years old (±1.8yrs), before the recruitment, subjects are screened for neurological conditions as well as contraindications for MRI.

2.2 Experimental design and Data acquisition

Subjects are guided to performed repetitive simple movements of different body parts in independent session: 1) thumb flexion/extension, 2) index flexion/extension, 3) little finger flexion/extension, 4) elbow flexion/extension, 5) foot flexion/extension and 6) tongue protrusion/intrusion. Within each session, blocks of 'movement' and 'rest' are interleaved, with seven 10-second movement-blocks alternating with seven 20-second rest-blocks (Figure 12). Each type of movement is performed in two separate sessions, and sessions of 6 different movement types are counterbalanced. At the beginning and the end of each movement-block , visual signals of go and stop are delivered though a screen placed at the end of the MRI scanner tunnel. Between conditions, subjects are instructed by the experimenter outside the scanning room through microphone.

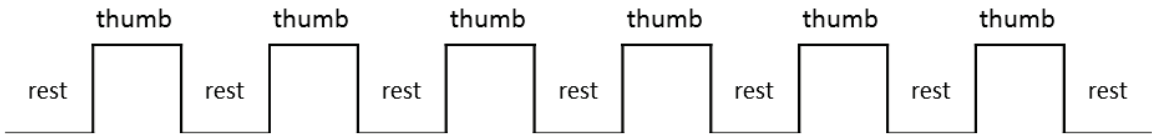

Figure 12. Experimental design. Individuated movement is performed in each independent session (e.g. thumb abduction/adduction). Movement blocks are interleaved with rest blocks, each block lasts 10s. Within each block, movement is executed for 10 seconds.

Functional whole-brain imaging was performed using a Bruker Medspec 30/80 AVANCE (Bruket®, Ettlingten, Germany), with an 8-channel phased-array head coil. Each acquisition

included 160 (to be changed) dynamic scans, using a gradient-echo echo-planar sequence sensitive to blood-oxygenation level-dependent (BOLD) contrast. Sequence parameters were: TR = 3000 ms, TE = 35 ms, matrix size 64 x 64, 35 slices, slice thickness 3 mm, field of view 192x192mm.

An anatomical image was also acquired for each subject using a sagittal 3-dimensional T1-weighted MPRAGE sequence covering the whole brain volume (field of view 256x230x180mm^3, matrix 256x192x104, TR/TE/flip angle 25 ms/5 ms/20°, slice thickness 1 mm).

1.3 MRI data analysis

The fMRI data are analyzed to answer two main questions: 1) the functional organization in in each sensory- and motor-related brain region, in terms of center of gravity (COG) and of activation volumes, and 2) the effect of different body part on the COG and volume overlapping.

Firstly, in order to describe the functional organization, random effect of each movement type is explored within each region of interests (ROI), namely M1, S1, SMA, SPL and IPL, separately. Then, COGs of significant clusters in each cluster is computed to demonstrate the functional organization. It has been proposed that COG is more reliable value than peak activation across sessions in somatotopic study(Alkadhi et al., 2002), and it has been used widely in many fMRI studies to indicate the location of the neural representation underlying simple movement (Indovina and Sanes, 2001; van der Zwaag et al., 2013) .

Tunctional organization is also analyzed in terms of activation volume. To this end, we merge the significant activation volumes of all six movements in a same anatomical map by using winner-take-all procedure in 3D space to determine the category of each voxel significantly activated by the movement of more than one body part.

Although as we have introduced above, in previous fMRI studies (Indovina and Sanes, 2001; Olman et al., 2012; Rao et al., 1995), independent COG supports the view that simple movement is represented in the sensory- and motor related brain regions, whileas the extensive spatial overlap between the activation volumes of different body parts seems to complicate this view, there has not been any good explanation on these observations. However, according the

hypothesis of synergetic control of M1, overlapped volumes could reflect the spatial overlap of motor synergies in M1.

Thus, secondly, in this study, in order to explore the effect of different body part (movement type) on COG and volume overlapping, individual data, which include the individual values of COG and statistical parameter maps of significant volumes under all six movement conditions separately, are pooled into statistical analysis. Detailed description of the data analysis is as following.

1.3.1 Preprocessing of fMRI data

We used Matlab 7.1 and SPM toolbox (version 12) (http://www.fil.ion.ucl.ac.uk/spm/) to analyze fMRI data.

Before preprocessing, the first 5 volumes of each scanning session are discarded to avoid the disequilibrium of signal at beginning of the scan.

First, 'slice timing' correction is performed to correct the slightly time discrepancy when collecting each slice of a volume (Kiebel et al., 2007). All slices are resliced according to the acquisition time of the middle slice.

Then, it is very important to correct motion in our data set because the task require repetitive movements through the session. One of the task demand is tongue protrusion/intrusion that may especially increase the head motion between volumes. Thus, we perform a 'realignment' procedure to correct motion of our dataset (Friston et al., 1995). The translations and rotations of each volume are estimated. Sessions with translations more than 3mm and rotation more than 3 degrees will be discarded.

Third, intra-subject registration is performed in order to match the position of structural scan (the anatomical images) and the functional images. Co-registered structural image will be used later to normalize functional images.

The fourth step is to perform inter-subject registration to match subjects. This is realized with normalization procedure of SPM (Ashburner, 2007).

At last, to increase the signal-to-noise ratio and improve the ability to detect true activation in the following statistical process, we use a 6mm- width Gaussian kernel for spatial smoothing .

After above steps of preprocessing, imaging data are ready for further statistical analysis.

1.3.2 Definition of ROI

This experiment aims to explore the representations of voluntary individuated movement in motor-related brain regions, and to compare the structure of their organization across these brain regions.

Based on the cytoarchitectonic and functional variances, M1 has been proposed to have two different subregions, namely area 4a and 4p (figure 12)(Geyer et al., 1996)(Binkofski et al., 2002). The same methodology has been used to delineate complex subregions of S1(Geyer et al., 1999, 2000; Grefkes et al., 2001), SPL (Scheperjans et al., 2008) and IPL (Caspers et al., 2006, 2008). In this study, we performed small volume correction with each of these regions of interests. To generate masks for small volumes, we adopted the atlas based on the probabilistic cytoarchitectonic map (Eickhoff et al., 2005, 2006a, 2007a) in Anatomy toolbox. Although this atlas is being updated to include more brain regions, however, we were not able to have SMA with the it the moment we were performing this analysis. Thus, alternatively, the volume of SMA was determined from the newly released atlas used in SPM12 toolbox.

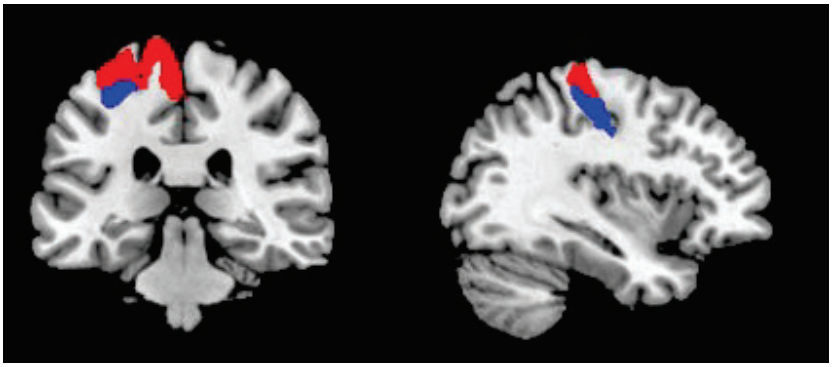

Figure 12. Coronal (left) and axial (right) illustration of two architectonic subdivisions in M1, area 4a (red) and 4p (blue). Figure is made according to the subdivision by Forschungszentrum Jülich GmbH (Geyer et al., 1996)(Eickhoff et al., 2005).

1.3.3 Statistical analysis of fMRI data on individual level

A general linear model (GLM) of design matrix is specified for each movement condition for each subject. Estimation of statistical parameters is performed based on GLM model using

classic approach. Then, one sample t-test is performed to explore movement-specific activation by contrasting the movement with rest phases. In the end, thresholding procedure with false discovery rate (FDR) at 0.01 and minimum cluster size of 10 voxels is applied on individual statistical parametric map (t map) to determine significant activated voxels and clusters. Thresholding procedure is performed within each ROI, namely M1, S1, SMA, SPL and IPL.

a) ***Center of gravity*** is defined by 3D MNI coordinates, in which the x, y and z-axis indicate the medio-lateral, antero-posterior and supero-inferior planes respectively. It has been widely used to describe the pattern of somatotopic arrangement and has demonstrated high intra-session reliability (Alkadhi et al., 2002). In our study, the COG of each significant cluster is computed using home-written Matlab function.

b) ***Overlapped voxels*** of two or more movement types are attributed to the one with highest t value in this voxel. This '*winner-take-all*' method provides arbitrary description of the functional organization patterns within one ROI, especially when movement type specific activations overlapped extensively. This method has been adopted in previous studies and demonstrates somatotopic arrangement similar with that from Penfield's stimulation study (Meier et al., 2008)

c) ***Volume overlapping.*** In order to explore the character of volume overlapping across brain regions, we introduced an index to demonstrate the level of overlapping, in the following part of the thesis, I will use the term 'ratio of overlapping' (RO%) to indicate it.

RO% = Number of overlapped voxels/ Total number of activated voxels

Within each ROI, ROs within-limb and between limb were calculated, which were the RO between each two fingers, between one of three fingers with elbow, between one of three fingers with tongue, between elbow and tongue, separately.

1.3.4 Second level analysis

In order to explore the random effect of movement type, factorial design is defined in the second level analysis in SPM for each movement condition independently. Contrasts between movement and rest phase of each subject from first-level analysis were put into the design matrix,

and the t test is conducted to explore significant activation volumes specific to each movement type.

In the end, thresholding procedure with false discovery rate (FDR) at 0.01 and minimum cluster size of 10 voxels is applied on individual statistical parametric map (t map) to determine significant activated voxels and clusters. Thresholding procedure is performed within each ROI, namely M1, S1, SMA, SPL and IPL.

1.4 Statistical analysis in group

In the group level analysis, peak activation could be located in each ROI for each type of movement. The brain voxel with peak activation indicates where the most prominent BOLD signal change occurs, and the activation volume could reflect a concentration of neuronal population underlying the control of a specific cognitive function. However, in previous literature, it has been demonstrated that that the coordinate of peak activation is less robust than the geographic center of the activation volume across sessions. Thus, in the following, any discussion on the functional organization will be based on COG.

In order to explore the effect of movement type on COG and effect of ROI on RO, further statistical analysis is performed with Statistica software, using individual values from the above first level analysis, which were the individual COG of each movement type, and the RO in each ROI.

1.4.1 The effect of movement type on COGs within each ROI

In each ROI, repeated ANOVA is performed to explore the effect of movement type on the x, y and z value of COG respectively. This analysis is aimed to determine whether representations of different body parts are separable, thus provide statistic evidence on whether there is somatotopic arrangement in that particular brain region.

1.4.2 The effect of ROI on volume overlapping

In order to examine the existence of significant volume overlapping for each pair of movement types (as described in 2.3.3) within each ROI, firstly, we performed one-sample t test with individual RO%.

Secondly, for those pairs of movements that were significantly overlapped, to examine whether the level of volume overlapping differs across brain regions, we performed repeated ANOVA with ROIs as the factor.

3. Result

In this experiment, we found that *1)* significant functional representation of simple movements exist not only in contralateral M1, S1 SMA, but also in higher cognitive region IPL; but in SPL, only elbow movement elicited significant changes in BOLD responses; *2)* in M1, within-limb, representation of fingers and elbow overlapped extensively, with winner-take-all procedure, activation volumes of fingers interleaved, while activation volumes of elbow lies superior to *those* of fingers; *3)* in M1, fingers have innervation of common intrinsic muscle don't exhibit higher RO% than fingers don't have; *4)* the arrangements of COGs in IPL indicate that somatotopic organization exists but with different structures as in M1, such as single repetitive movements of fingers don't generate independent representation, and the representation of mouth is close to the representation of upper limb.

The activation volumes specific to each movement type distributed at contralateral M1 S1, PM and SMA, as well as parietal cortex, are shown in **Figure 13.**

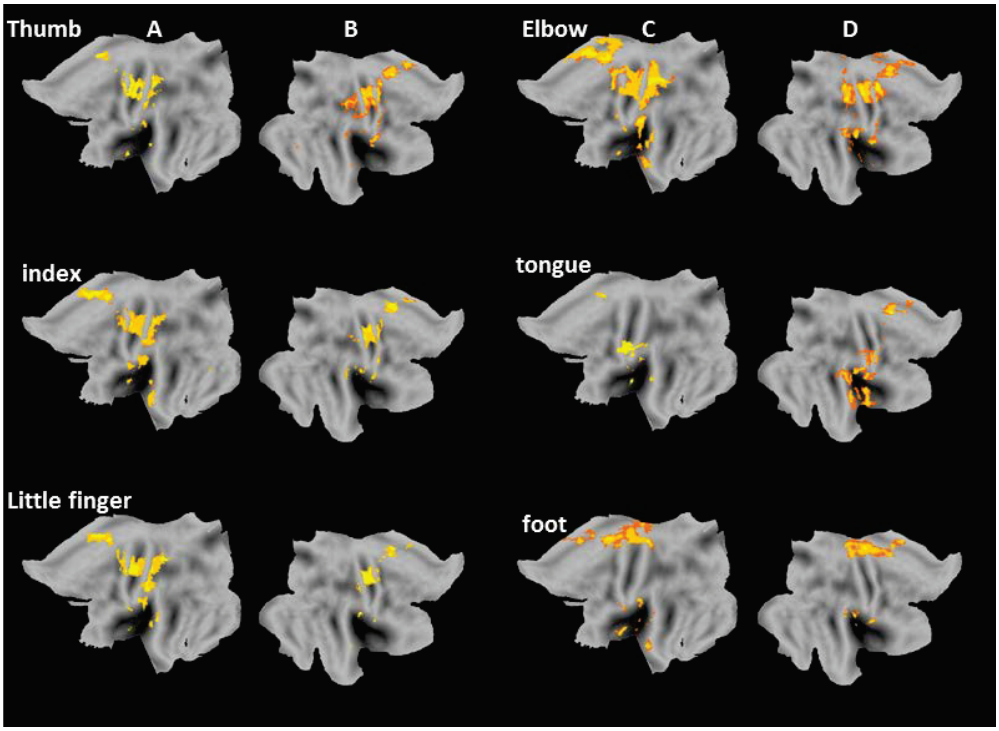

Figure 13. Activation volumes of left- (column C and D) and right-side (column A and B) individuated movements.

3.1 Movement-specific activations in motor-related brain regions

3.1.1 representations of simple movements in M1: COG and activation volumes

The 2nd level analysis of fMRI data indicated that all six movements of both the left- and right-side elicited significant changes of BOLD responses in contralateral M1(FDR 0.01, cluster size>10 voxels) (table 1). According to the anatomical and functional subdivision of M1 by Geyer and the followers (Caspers et al., 2006; Geyer et al., 1996), the peak activation of foot lies uniquely on the medial surface of precentral lobe which is considered as area 4a; for elbow and the three fingers, each has two activated clusters with one lies in 4a and the other in 4p; mouth movement has one single activation centered in area 4p (table 1).

Table 1. Coordinates of peak activation and volume size in M1 (area 4a and 4p)

	Left hemisphere		Right hemisphere	
	Peak activation (x,y,z)	Nb.Vx*	Peak activation (x,y,z)	Nb.Vx
Thumb	-33, -20, 46	63	33, -29, 52	69
	-39, -26, 58	45	42, -23, 55	20
Index	-36, -32, 58	54	33, -26, 52	56
	-36, -27, 61	43		
Little finger	-36, -20, 52	57	33, -23, 49	45
	-39, -17, 52	45	42, -23, 55	13
Elbow	-36, -34, 61	61	30, -29, 55	48
	-36, -39, 66	61	27, -29, 67	54
Tongue	-57, -8, 31	16	54, -5, 28	15
Foot	-15, -35, 73	143	3, -26, 67	137

* Nb.Vx, number of voxel.

As described in the method, COGs are used to describe the geographic location of each movement representations and to make statistical comparison (table2). Non-parametric ANOVA revealed that, for both left and right-side movements, movement type has significant effect on COG on contralateral M1 at all three axis in the MNI space (right-side movement, x-axis,

X^2(4,N=10)=36.2, p<0.001, y-axis, X^2(4,N=10)=35.04, p<0.001, z-axis, X^2(4,N=10)=34.96, p<0.001; left-side movement, x-axis, X^2(4,N=4)=13, p<0,05; y-axis, X^2(4,N=4)=15.2, p<0.01; z-axis, X^2(4,N=4)=14.6 ,p<0.01).

These results indicate that in M1, 1) the structure of functional localization of simple movement revealed in fMRI study mirrors the classic somatotopy described by Penfield (Penfield and Boldrey, 1937) and others. In general, foot lies most superior and caudal at the paracentral lobule, while the tongue localizes in most ventral and rostral portion the lateral surface of precentral lobe; 2) within-limb, the geographic centers of small body parts, such as individual finger and elbow, also arranged in somatotopic order**(see table 2, figure 14, figure result 14)**.

Table 2. COGs of each simple movement in M1 (area 4p and 4a) on group level.

	Area	Right-side movement (x,y,z)	Left-side movement (x,y,z)
Thumb	4p	-35, -25, 50	36, -24, 48
	4a	-37, -27, 59	37, -30, 60
Index	4p	-35, -26, 51	36, -24, 49
	4a	-37, -27, 59	NaN
Little finger	4p	-34, -26, 51	36, -23, 49
	4a	-37, -27, 59	37, -28, 60
Elbow	4p	-34, -27, 52	35, -25, 51
	4a	-30, -28, 61	26, -30, 62
Tongue	4p	-51, -10, 31	49, -11, 33
Foot	4a	-7, -32, 67	7, -31, 68

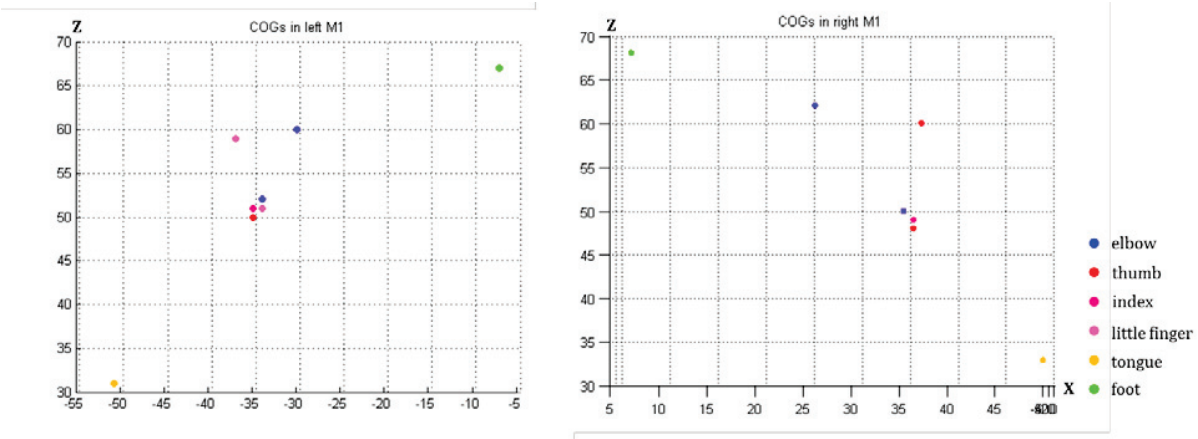

Figure 14. COGs in contralateral M1 of right-side (A) and left-side (B) simple movements.

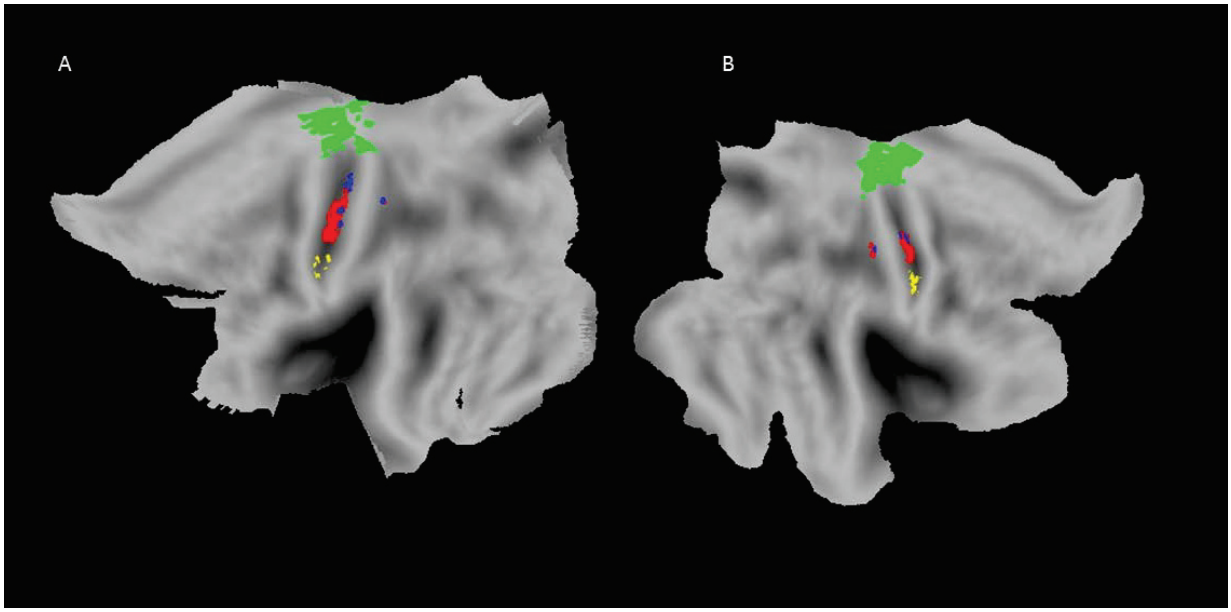

Figure 15. Activation volumes in contralateral M1 of right-side (A) and left-side (B) simple movements. Red, fingers; blue, elbow; green, foot; yellow, tongue.

However, considering the arrangement of activation volumes, within-limb , small body parts do not exhibit a strict somatotopic order **(figure 16).** In this map, activation volumes of three individual fingers *1)* overlapped extensively and *2)* interleaved to exhibit no somatotopic order. In fact, the activation volume of elbow lies superior to three fingers and forms a core-surrounding structure.

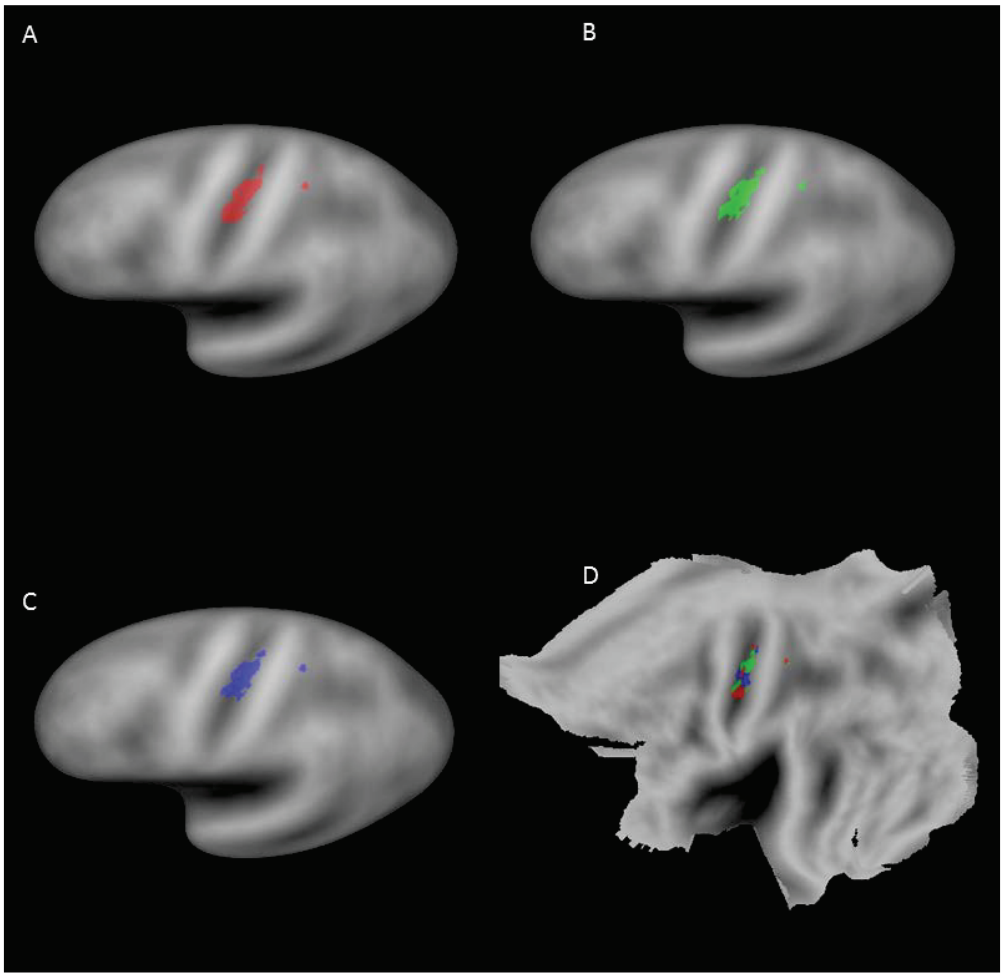

Figure 16. Activation volumes of individual thumb(A), index(B) and little finger (C) movements in M1. Extensive overlapping exists among three fingers. Interleaved volume representation is shown for three fingers after winner-take-all procedure (D).With winner-take-all procedure, each overlapped voxel is assigned to the movement type with highest t value, indicating higher neural activity in this voxel for that movement type. Red, thumb, green, index, blue, little finger.

Within-limb, fingers representation also overlapped extensively with that of elbow (**Figure 17**). However, after winner-take-all processing, the representation of elbow doesn't interleave with those of fingers, but lies superior to them.

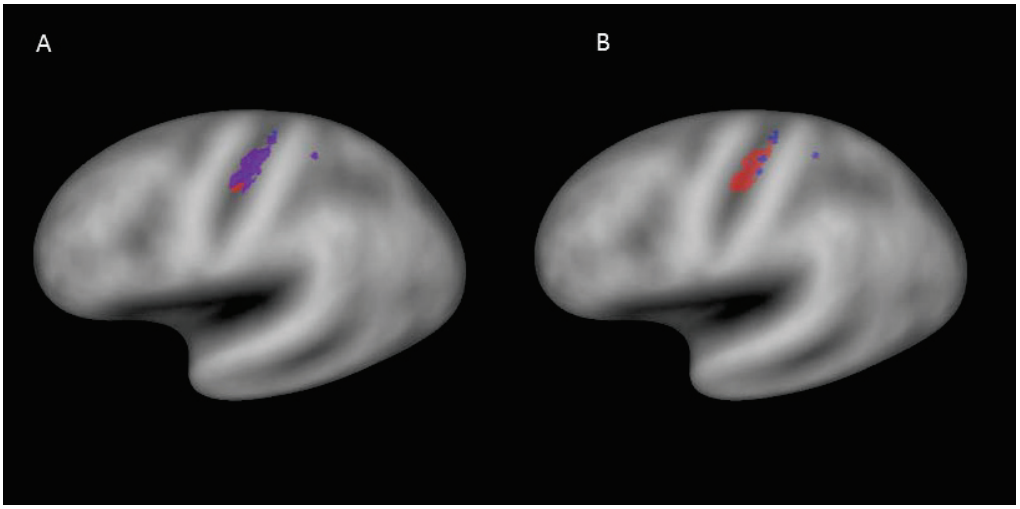

Figure result 17. Activation volumes of 3 fingers(red), elbow (blue) in M1. Extensive overlapping (purple) exists between fingers and elbow (A), after winner-take-all procedure, overlapped voxels are mostly assigned to finger movement.

First, these results are consistent with the well accepted somatotopy in M1 that arrangement between limbs follows the order of peripheral body parts, however, within the large subregions, for example the hand in our experiment, fingers are not arranged in sequential order. Second, we found an interleaved pattern of individual fingers, which is similar with the neurophysiological findings in primate and has not been well described in human .This implicates similar functional basis of human M1 in generating motor output as of primate (Rathelot and Strick, 2009). Third, we didn't find any overlap between the representations of upper extremity and tongue, this is not consistent with the DES finding that implying the existence of hand/mouth synergy (Desmurget et al., 2014). In the end, the 'homunculus' pattern is also not significant in our result, since we didn't find a significant larger activation volume of thumb than the other two fingers(table 1).

This kind functional organization in M1, orderly arranged COGs and interleaved activation volume, could be the neural basis of skilled simple movements such typing and skilled coordinate movements such as reaching to grasp .

3.1.2 Representations of simple movement of in S1: COGs and activation volumes

All six simple movements of both the left and right sides of the body, elicited significant changes of BOLD responses in S1 (FDR 0.01, cluster size>10 voxels)(table3).

Table 3. Coordinates of peak activation and volume size in S1 on group level

	Left Hemisphere		Right Hemisphere	
	Peak activation (x,y,z)	Nb.Vx*	Peak activation (x,y,z)	Nb.Vx*
Thumb	-33, -35, 46	219	48, -20, 34	174
Index	-33, -35, 52	225	42, -20, 52	36
Little finger	-33, -41, 61	236	42, -20, 46	51
Elbow	-36, -44, 61	306	33, -38, 55	155
Tongue	-57, -8, 28	80	48, -20, 31	78
Foot	-12, -38, 58	10	9, -44, 67	10

* Nb.Vx, number of voxel.

Table s01. COGs of each simple movement in S1 on group level.

	Right-side movement (x,y,z)	Left-side movement (x,y,z)
Thumb	-42, -29, 50	43, -27, 47
Index	-43, -29, 49	44, -24, 50
Little finger	-42, -30, 50	45, -21, 48
Elbow	-39, -31, 52	33, -37, 56
Tongue	-54, -14, 32	54, -12, 29
Foot	-12, -39, 62	11, -42, 65

Non-parametric ANOVA demonstrated that movement type has significant effect on the location of COG on all three axis (x-axis, $X^2(5,N=6)=24.6$, p<0,001; y-axis, $X^2(5,N=6)=26$, p<0,001; z-axis, $X^2(5,N=6)=20.4$, P<0,01) for right-side individuated movements, and on two of the three axis for left-side movement (x-axis, $X^2(5,N=5)=10.8$, p=0.055; y-axis, $X^2(5,N=5)=14$, p<0,05; z-axis, $X^2(5,N=5)=13.9$, p<0,05), indicating somatotopic representations of simple movements in S1. Further post-hoc analysis demonstrated independent functional localization of

thumb and little finger on Y axis (Wilcoxon rank test, $Z=2.4, p<0.05$) of right hand, but not of left hand.

The functional localizations of six simple movements in S1 in terms of COGs have similar structure with that in M1, for both sides of movement **(Figure 18)**. In S1, 1) foot representation localizes in most dorsal and caudal part of S1 while mouth representation lies on the most ventral and rostral region, 2) fingers and elbow representations lie in between. This mirrors the classic map of Penfield's and others (Penfield and Boldrey, 1937). Differently, the COGs of simple repetitive finger movements are not as segregated as in M1, showing as that only the right-side thumb and little finger movements evoked separable COGs, but no other fingers pairs having distinct COGs.

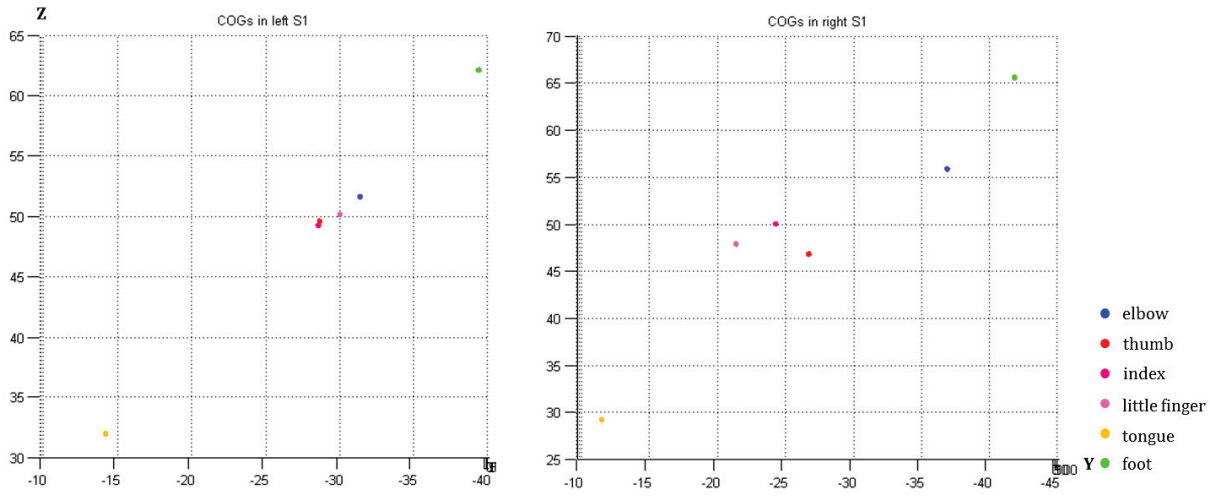

Figure 18. COGs of each simple movement in S1, on left and right hemisphere.

Considering the activation volumes, first, similarly as in M1, within the hand region, thumb, index and little finger overlapped and interleaved **(Figure 19)**. Also, differently, these activation volumes of upper limb are much larger in volume size (table 3) than those in M1, with the foot activation having the smaller size which is just the opposite as in M1(see in table1 and table 3).

These results are consistent with other MRI study, in which the neural representations elicited by simple movements are different in M1 and S1(Hluštík et al., 2001).

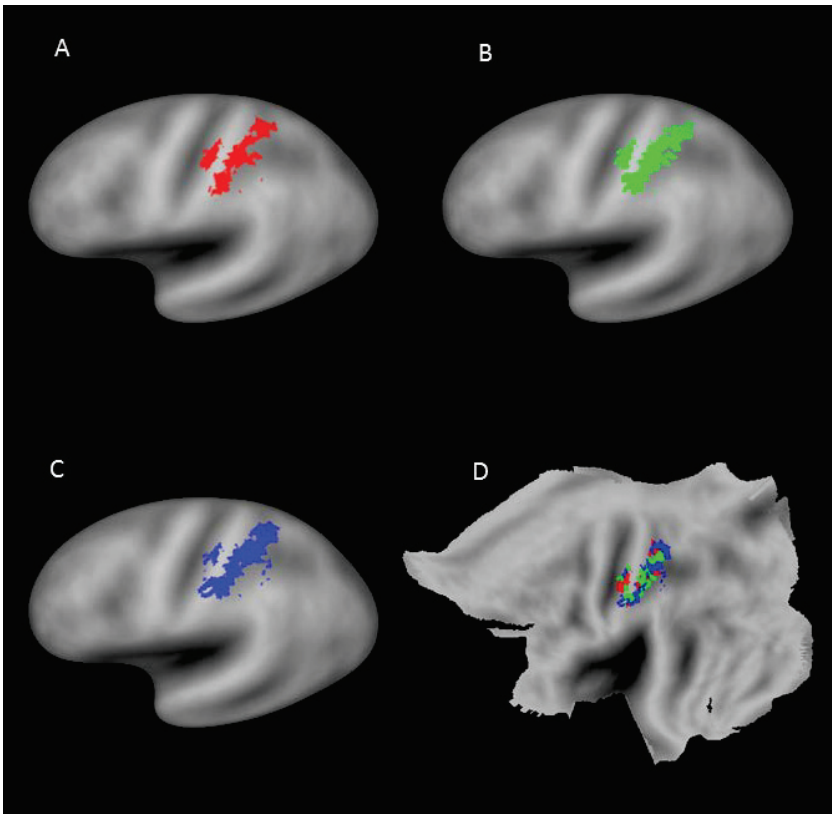

Figure 19. Activation volumes on left S1 evoked by right-side repetitive simple movements of little finger separately(A-C) and the arrangement after winner-take-all process (D). Red, thumb, green, index, blue, little finger.

3.1.3 Representations of simple movement of in parietal cortex

In parietal cortex, repetitive simple movements evoked significant changes of BOLD response in both SPL (table 5) and IPL (table 6). But SPL is less excitable than IPL by this kind of simple motor task, because only elbow movement has significant functional representation on both sides of the SPL. This result resembles the findings in primate, when monkeys were guided to perform simple, non-objected related movement, no motor responses could be recorded from the parietal cortex (Rozzi et al., 2008). Therefore, further analysis focus on the IPL.

Table 5. Coordinates of peak activation and volume size in SPL

	Right body		Left body	
	Peak activation (x,y,z)	Nb.Vx	Peak activation (x,y,z)	Nb.Vx
elbow	-30, -44, 55	124	24, -47, 70	35
	-6, -29,46	29		

Table 6. Coordinates of peak activation and volume size in IPL

	Right body		Left body	
	peak activation (x,y,z)	Nb.Vx	Peak activation (x,y,z)	Nb.Vx
Thumb	-48, -32, 31	10	51, -32, 43	24
			54, -29, 25	42
Index	-54, -29, 19	26	66, -26,22	51
	-48, -23, 34	42		
Little finger	-54, -26, 28	103	NaN	NaN
elbow	-51, -32, 19	73	60, -29, 22	164
	-54, -26, 43	43		
tongue	-54, -26, 34	16	60, -32, 16	111
			48, -20, 28	12
foot	-60, -29, 16	35	69, -29, 19	49

First, IPL has relative complete functional representations on both hemisphere.

For the right-side movements, on individual level, 3 of 12 subjects who had significant activation of little finger movement displayed two activation volumes of it,1 of 12 subjects who had significant activation of index finger displayed two activation volume of it , and 6 of 12 subjects who had significant activation of elbow movement displayed two activation volumes of it. Further, 2nd level analysis of fMRI data showed that all of the six right-side movements have significant activation on contralateral IPL (table 6), within them, only simple index and elbow movements have double activation volumes in IPL (Figure 20). Thus, during statistical analysis, for elbow movement, we consider the activation volume closer to IPS as cluster 1 (mean COG $\bar{X}$=-55, $\bar{Y}$=-31, $\bar{Z}$=30)and the other as cluster 2 (mean COG $\bar{X}$=-49, $\bar{Y}$=-50, $\bar{Z}$=20)for 6 subjects who have double representations of it. Also, non-parametric ANOVA indicated that the COGs of three fingers movements demonstrate no significant difference at any of the three axis in MNI space ($\bar{x}_{thumb}$=-56, $\bar{x}_{index}$=-57, $\bar{x}_{little\_finger}$=-56; $\bar{Y}_{thumb}$=-28, $\bar{Y}_{index}$=-29, $\bar{Y}_{little\_finger}$=-27, , p=0.5; $\bar{Z}_{thumb}$=32, $\bar{Z}_{index}$=33, $\bar{Z}_{little\_finger}$=34, Friedman-test by rank, p=0.7), therefore, in further statistical analysis, we consider the overall activation of three fingers as 'fingers movement', and the COG of finger is used in the comparison with elbow, tongue and foot in the following between-limb analysis (see in table 7 and figure result 20). Non-parametric ANOVA between-limbs revealed significant effects of movement types, namely fingers, elbow_c1, elbow_c2, tongue and foot, at x- (X^2(4,N=5)=10.1, p<0.05), y- (X^2(4,N=5)=13.6, p<0.01) and z- (X^2(4,N=5)=15.5, p<0.01) axis separately, indicating somatotopic arrangement of fingers, elbow, tongue and foot in left IPL.

Table 7. COGs of each movement and corresponding architectonic subdivisions in left IPL.

	COG (x,y,z)	Anatomical Label	Nb.Vx	Volume extent (most)
Tongue	-55 -24 37	PFt	16	73.6% in PFt
Finger	-51 -27 30	PFt	139	47.3% in PFt
Elbow	-52 -26 39	PFcm	78	38.3% in PFcm
	-54 -31 21	PFt	40	65.8% in PFt
Foot	-56 -30 19	PFop	35	33.8% in PFcm

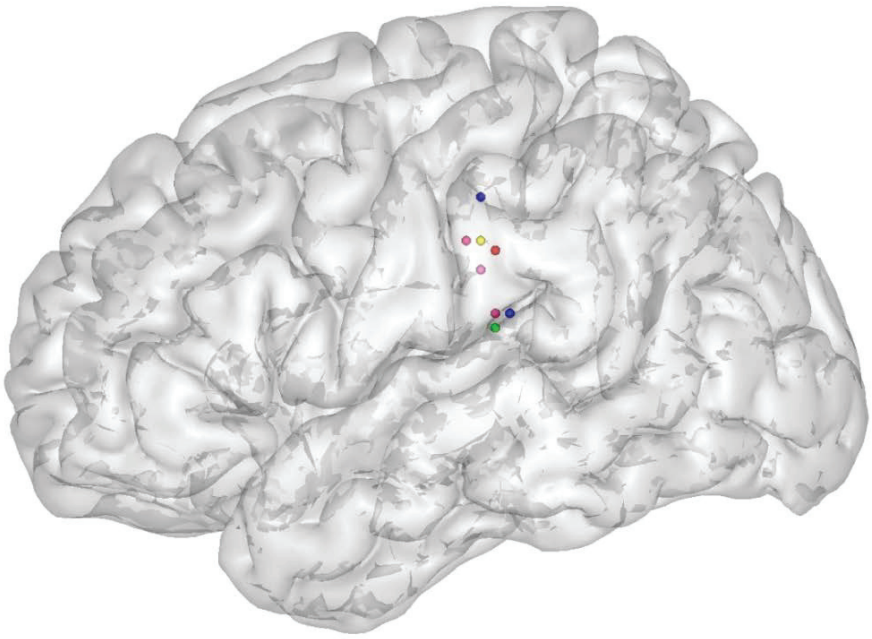

Figure 20. Peak activations of all six simple movements on left IPL.

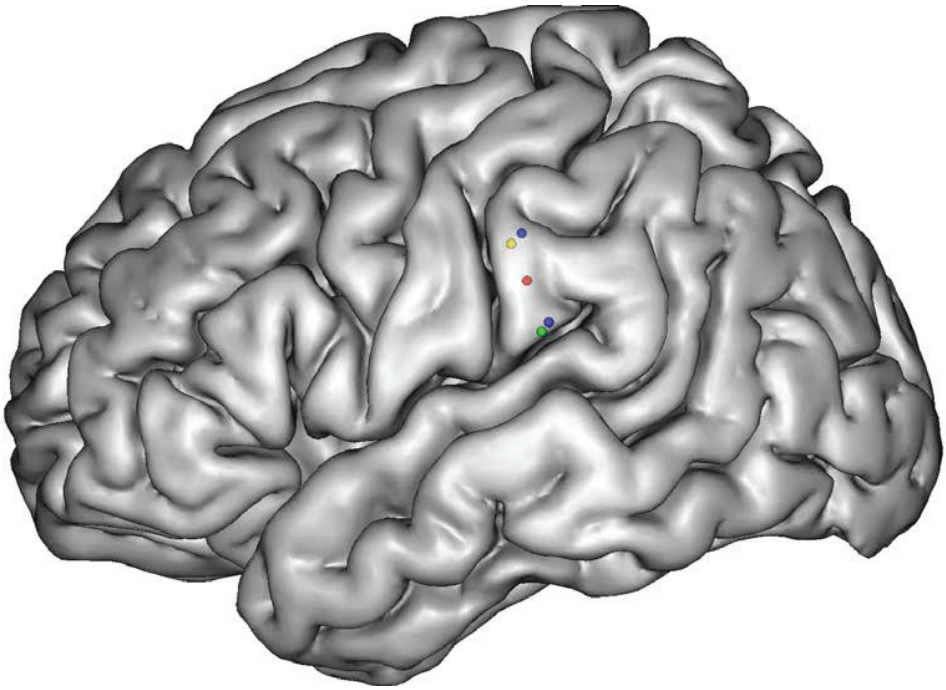

Figure 21. COGs of fingers, elbow, tongue and foot of right side movements on left IPL.

This result indicates a complete somatotopic arrangement of the neural responses of repetitive simple movement, including fingers, elbow, tongue and foot, in the most anterior subdivisions of IPL (Caspers et al., 2006, 2008). This map is different from the motor response maps from primate study, within which recorded motor responses distributed along the IPL(both PF and PG regions), but similar with the somatosensory map in primate's IPL that concentrates in the PF region.

Activation volumes also overlap in IPL. Within limb, representations of elbow overlap with and surround representation of fingers (**Figure 22A**). Interestingly, the representation of simple tongue movement lies within the region of fingers. This kind of organization probably relates to the role of IPL in action intention and organization.

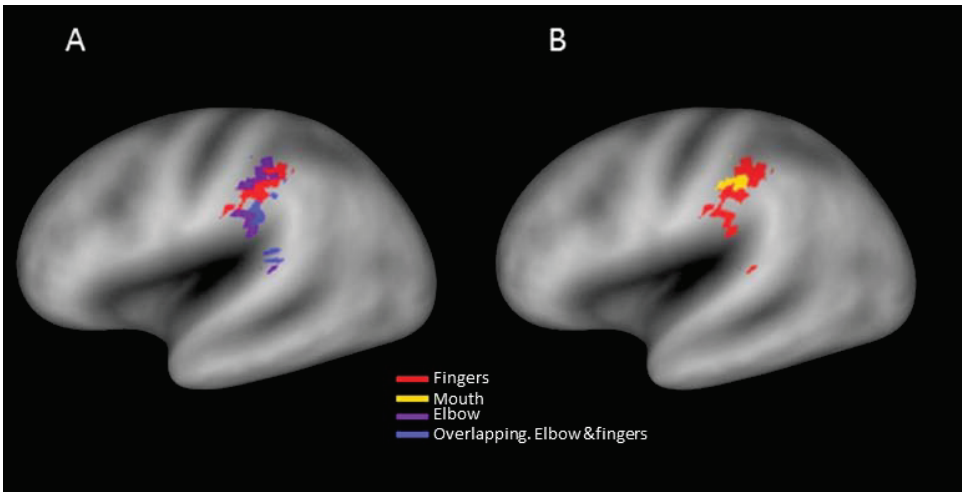

Figure 22. Representations of fingers and elbow movement (A), fingers and mouth movement (B). Activation volumes overlapped extensively between fingers and elbow (A), and between fingers and mouth (B).

In summary, four findings in IPL are of particular interests, *1)* repetitive extension/flexion of individual finger doesn't have independent functional representations in IPL; *2)* neural response of repetitive simple movements of fingers, elbow, mouth and foot have are organized in somatotopic manner in contralateral PFt and PFcm regions, which are the two most rostral architectonic subregions of IPL (Caspers et al., 2006), 3) repetitive simple movement of elbow has double representations that surrounds the representation of finger 19 and 20) differently with in M1 the representation of mouth has significant overlap with that of fingers in IPL (figure result 22 B).

3.2 Volume overlapping across motor-related brain regions

In fMRI studies intending to localize the functional specialty of simple movement, one prominent feature is the extensively volume overlapping within each motor and sensory-related brain region, such as in M1, S1, PM and SMA.

In this study, with 'winner-take-all' method (see in method), we managed to make an arbitrary illustration of the somatotopy of the six simple movements within the territory of each ROI (Figure 23). Although with this computation, some information like the effect of multiple movements in single voxel is concealed(Meier et al., 2008) this illustration could still demonstrate some basic features functional organization, 1) in contralateral M1, foot, elbow, fingers and tongue are represented progressively from dorsal to ventral portion of precentral lobe, and the fingers entangling without sequential order but represented a interleaved pattern of organization with finger interleaved within the hand region; 2) in contralateral S1, similar dorsal to ventral organization also exists, but the activation volumes are larger and with different proportion between body surface and volume size as in M1; 3) in IPL, simple movements of large body parts such as hand, elbow, tongue and foot, also have distributed representations in the most anterior PF regions , also, we found significant overlap of activation volume between tongue and hand that is not represented in M1.

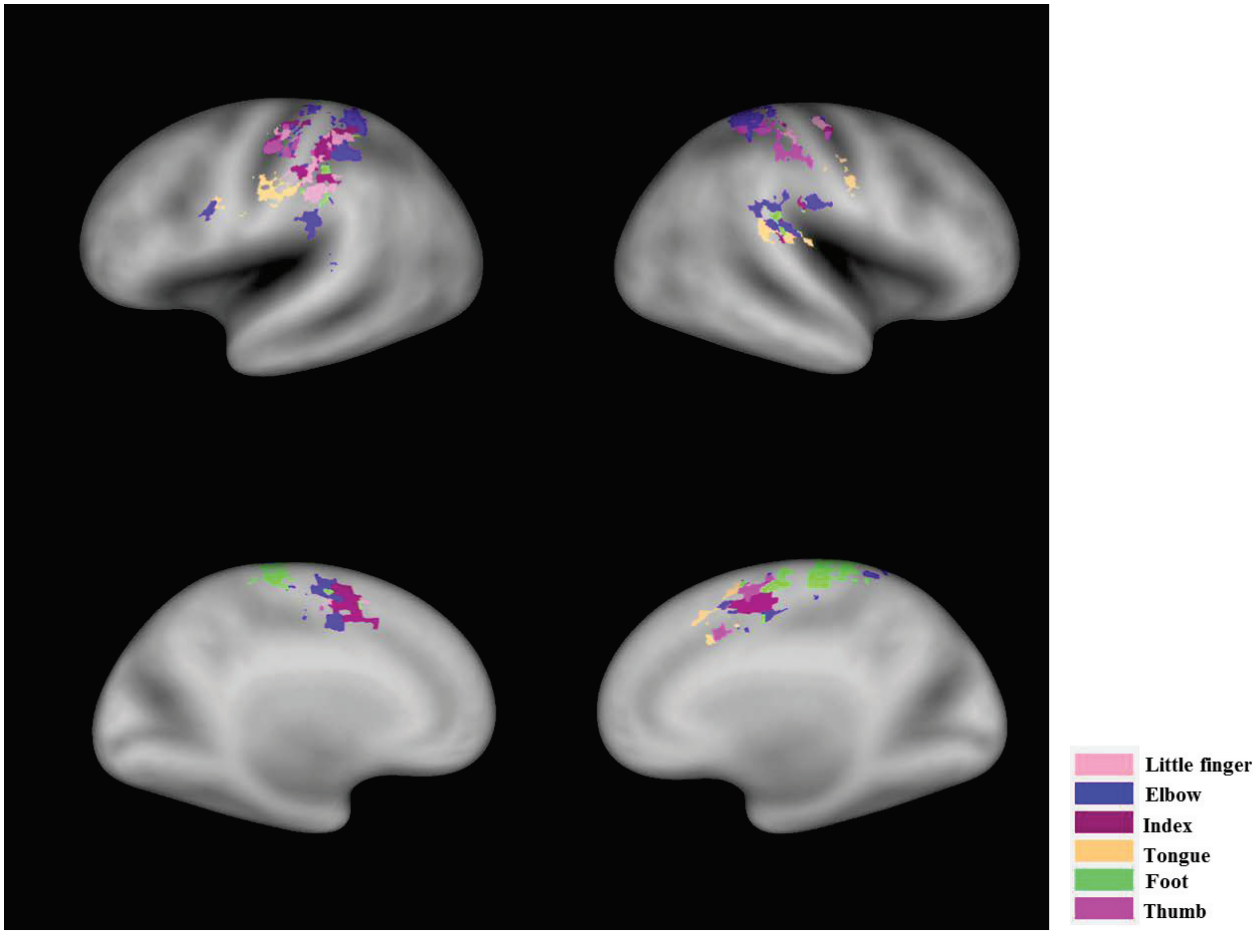

Figure 23. Somatotopic organizations of six simple movements across multiple motor-related brain regions. The category of overlapped voxels is determined by 'winner-take-all' procedure.

3.2.1 Volume overlapping within-limb

RO% of three fingers, as well as between pairs of fingers, are computed separately for each subject using home-written Matlab function. Within the overall activation region of all three fingers in each ROI, those voxels which are activated by more than one finger movements are assigned to the finger with the highest t value in this voxel. In this way, we computed the mean RO for each ROI for left and right hand separately.

Although in M1, simple repetitive flexion/extension of individual finger could evoke independent representations in terms of COG, is it appropriate to infer that movement is the basic unit underlying the organization in M1 in generating motor output? We further explored the volume overlapping of different finger pairs in M1, in order to test the hypothesis that if the volume overlapping simply implying the recruitment of common muscles between different movements, we could expected different degree of overlapping between different finger pairs. Repeated ANOVA indicates that, in area 4p, the values of RO% of thumb vs. index(65%), thumb.vs little finger(69%) and index vs. little finger (68%) are statistically identical. This result doesn't support the hypothesis that RO% reflects the neural response of commonly recruited muscle (**Figure 24**).

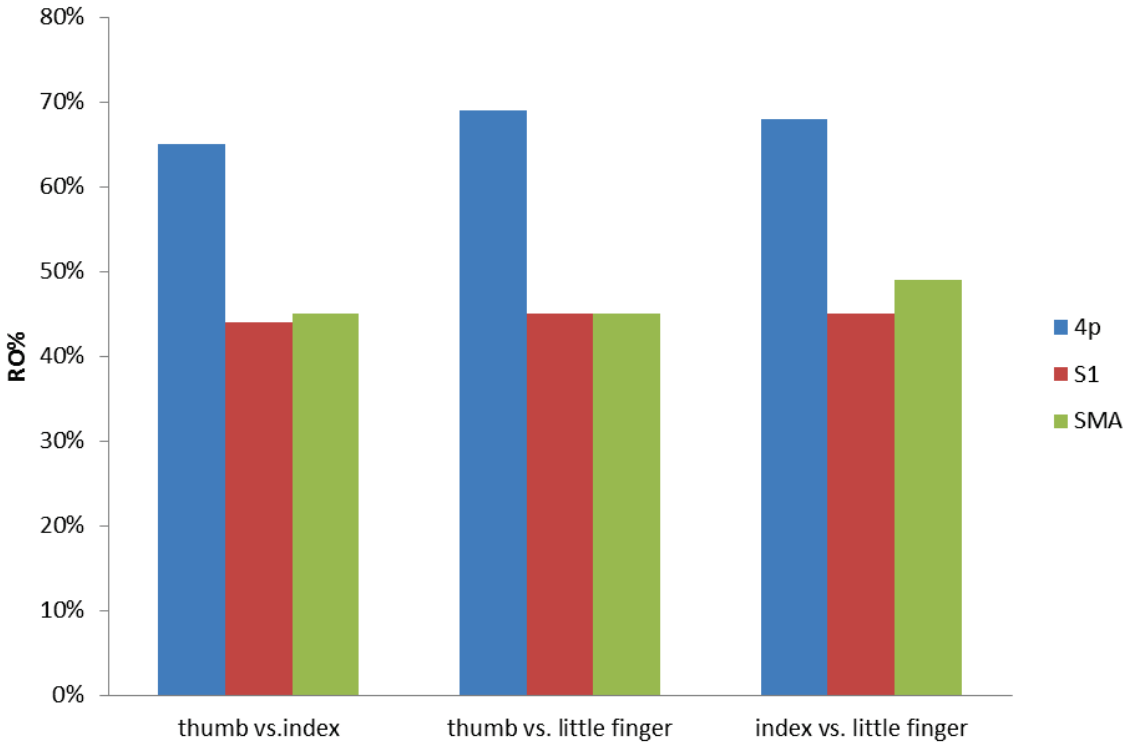

Figure 24. Volume overlapping (RO%) of each pairs of right-side finger movements across contralateral brain regions having independent representation of fingers. The category of overlapped voxels are determined by winner-take-all procedure.

Repeated ANOVA indicates that for all three finger pairs, RO% is significant higher in 4p than in S1 and SMA(thumb vs. index, $F(2,26)=7$, $p<0.01$; thumb vs. little finger, $F(2,24)=11.5$, $p<0.001$; index vs. little finger, $F(2,26)= 6.4$, $p<0.01$), which means that compared to M1, activation volumes of individual finger movements are more distributed and segregated in S1 and SMA, this is contradicted with the result of COG (see in part 3.2.1) (**Figure 23**).

Also, within limb, the representation of fingers and elbow overlapped in M1, S1, SMA, and IPL. Because there is no separable representation of individual finger in IPL, we compare only the individual finger and elbow in area 4p, S1 and SMA (**Figure 23**).

After, we examined the RO% of 3 pairs of fingers, namely thumb and index, thumb and little finger and index and little finger. Non-parametric ANOVA indicates that for right hand, ROI had significant effect on volume overlapping between thumb and index (X^2(2,N=14)=10.9, p<. 01), between thumb and little finger (X^2(2,N=14)=7.4, p<. 05), as well as on that between index and little finger (X^2(2,N=14)=7, p<.05) **(Figure 23)**. The cooperation of thumb with index is supposed to be more frequently than that of index with little finger, however, for the right hand, we didn't find any statistical difference on the ROs of the two pairs of fingers, on any one of the ROIs.Therefore, the volume overlapping between finger pairs on motor related regions can not reflect the difference on the movement coordination between finger pairs.

In summary, within-limb, the volume overlapping across five motor-related brain regions exhibits three main character, 1) overall speaking, both three fingers and finger-elbow pairs are less overlapped in IPL and SMA than in M1 and SMA, *2)* three digits overlap with equal amount in area 4p and S1, but overlapping between index and little finger are significantly higher than that other two finger pairing in SMA and IPL **(Figure 23)**; *3)* finger-elbow pairs overlap with equal amount in M1, S1, and SMA, however differently, in IPL index and little finger overlap with elbow more than thumb and elbow. These discrepancies of RO% across motor related regions implying that the neural basis underlying the representations of individuated finger movements in 4p and S1 might be different from that in SMA and IPL.

II.2 Study 2- Re-establishing the merits of electrical brain stimulation

Article I

Re-establishing the merits of electrical brain stimulation

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Abstract

In the past decades, direct electrical stimulation (DES) has been a key method not only in determining the organization of brain networks mediating movement, language and cognition but also in establishing many central concepts of modern neuroscience, such as the electrical nature of neural transmission, the localization of brain functions and the homuncular arrangement of sensorimotor areas. However, recent criticisms have questioned the utility of DES and argued that data collected with this technique may be flawed and unreliable. Like any other neuroscientific method, DES does have limitations. However, existing evidence argues strongly for its validity and usefulness by demonstrating that DES produces highly specific outcomes at well-defined anatomical sites and significantly minimizes post-operative deficits in brain-damaged patients.

Worthiness of Electrical Brain Stimulation: a long-standing controversy

Approximately 150 years ago Fritsch and Hitzig discovered that direct electrical stimulation (DES) of the cerebral cortex of dogs evokes localized, topographically organized muscles contractions in the contralateral hemibody [1]. This discovery led several researchers to use electrical stimulation to probe the anatomic and functional organization of the brain [2, 3]. David Ferrier was perhaps one of the most famous. Using DES in various animal species, he reported that complex, ethologically relevant movements were represented in specific cortical areas [4]. However, these results were promptly challenged by critics who argued that such a somatotopic arrangement was artifactual and related to some uncontrolled spread of current [2].

Strikingly, things have not really changed since the pioneering ages of DES. For the last century, this method has kept providing unique clinical and fundamental knowledge with regard to the anatomo-functional organization of the brain [5-11]. However, at the same time, critics have kept challenging the relevance of this knowledge [12-14]. Although formulated in contemporary terms, the core arguments against DES remain mostly similar to the arguments originally encountered by Fritsch, Hitzig, and Ferrier. They are centered around the idea that DES outcomes cannot be convincingly interpreted because the electrical current artificially delivered at a specific brain location has unknown effects at local and distant neural sites [13, 14]. In line with this reservation, some eminent neuroscientists gone as far as to wonder whether DES was an adequate tool for probing cortical functions [12].

The major strength of these criticisms, and the reason for their recurrence, lies in the fact that they are hardly falsifiable. Whatever the outcomes of a stimulation experiment, it is always possible to argue that DES acts through some unknown saturating, activating or inhibiting influences at local and/or distant sites. For instance, if a specific behavioral effect is observed

following stimulation of the parietal cortex, it is always possible to argue that this effect does not reflect a parietal involvement for the considered behavior but rather the role of some obscure remote region activated/inhibited through stimulation of axonal pathways [13]. No matter what one does, this type of argument is irrefutable [15]. However, does this status of irrefutability mean that the argument is likely or plausible? The aim of this review is to address this issue. Below, we argue that DES offers a unique opportunity to examine neural functions and hence to probe the anatomo-functional organization of the brain. We provide evidence that, even though DES is not devoid of limitations and shortcomings, the major recurrent criticisms faced by this method are essentially unfounded. When objectively evaluated, these criticisms appear to be, for the most part, unsupported by the actual effects of DES as they are reported in the clinical and basic neuroscientific literature. On the contrary, DES evokes reliable and highly specific outcomes that are unlikely to be artifactual and associated with an anarchic spread of current. In relation to this point, one may note that critics of DES often have a tendency to interpret the outcomes of electrical stimulation in isolation, without considering complementary observations provided by other methods such as neuroimaging or brain lesions [13]. However, such observations are essential for interpreting DES effects and distinguish between purely theoretical criticisms and objectively valid reservations.

DES and the sensorimotor system

In humans, several motor-related cortical areas (designated "*motor areas*" hereafter) have been shown to evoke movements when electrically stimulated [5], including the primary motor cortex (M1) [16], the primary somatosensory cortex (S1) [17], the premotor cortex (PMC) [6], the supplementary motor area (SMA) [18], and the cingulate cortex (CC) [19]. Interestingly,

these areas are widely interconnected with each other and they all have direct efferent projections to the spinal cord [20-23]. As a consequence, it can easily be argued that any artificial mix of direct and indirect activations can mediate any motor effect of electrical stimulation [12]. For instance, movements evoked by stimulating PMC can reflect a direct recruitment of the corticospinal projections emanating from this structure and/or an indirect activation of remote pathways originating from M1, S1, the SMA and CC [13].

Although there is no doubt that even single stimulation pulses propagate laterally through cortico-cortical connections [24], there is little evidence that this spread of current can evoke muscle activations through the recruitment of remote structures with descending projections to the spinal cord. This can be seen, for instance, in the fact that many parietal and prefrontal structures, known to be heavily and reciprocally connected with motor areas [25-28], do not trigger movements when electrically stimulated [29]. As initially shown by Penfield, in a large series of patients, the only cortical regions that consistently evoke movements in response to DES, in humans, have direct access to the spinal cord [5]. This observation is consistent with a recent study showing that the type of long train high-frequency electrical stimulation used in surgical mapping procedures in humans [30] tends to silence distant cortical sites, which predicts that functional activation of remote descending pathways will be prevented [31].

The claim that DES anarchically recruits direct and indirect descending pathways seems also hardly compatible with the functional specificity of the movements evoked by this technique. Indeed, in contrast to what has recently been suggested [14], DES effects are highly specific to the cortical region being stimulated [29]. Clearly, the argument of behavioral syncretism only holds, at first glance, when the functional characteristics of the evoked responses are disregarded. For instance, as shown in fine-grained studies, the motoneurons controlling upper-limb muscles

exhibit a distinct pattern of activations following stimulation of M1 or SMA [32, 33]. In the same vein, the movements triggered by stimulating the precentral gyrus or the cerebellar cortex are dramatically different. While stimulation of the cerebellar cortex evokes highly focal single joint responses [7], stimulation of the precentral gyrus often elicits complex multijoint synergies [6, 10, 34] (Figure 1). Interestingly, it has been suggested that these synergies could be the trivial biomechanical outcome of tetanically recruiting spinal interneurons (which would cause an artificial tonic cocontraction of the limb muscles). In support of this view, it was reported that upper-limb movements achieving a constant final posture were also evoked by stimulating the corticospinal tract at medullary levels [12]. This is true. However, the criticism overlooks two important facts. First, within the precentral gyrus, stimulation at different -but spatially close- sites evoke movements that have very different functional characteristics [35] (Figure 1), which would not be expected if these movements did represent a mere artifact of anarchically activating spinal motoneurons. In agreement with this claim, it has been shown, within precentral regions, that motor sites are organized in a manner that optimizes topographic continuity of common motor behaviors [36]. Second, complex movements triggered by stimulating the precentral gyrus and the spinal cord have fundamentally different characteristics. Movements evoked through spinal stimulation have no biological plausibility at all. They consist of brisk flexions of the entire limb, that are highly variable from trial to trial and occur with exorbitant latency (up to several seconds) [37]. By contrast, the responses elicited by cortical stimulation have short latencies, a high degree of inter-trial reproducibility and an electromyographic (EMG) pattern that is strikingly similar to the pattern of natural movements [10, 34]. In agreement with this point, one may emphasize that the complex movements reported following stimulation of the precentral gyrus are not arbitrary, as would be expected from a blind recruitment of motoneurons.

They have a clear ethological value [38], as can be seen clearly for hand-to-mouth synergies in which the closing hand to approach the face while the mouth is opening [10]. These synergies are already expressed by human fetuses during gestation, which makes it tempting to speculate that they are genetically prewired [39, 40]. If one assumes that this type of movements result from a simple spread of current, one should predict the occurrence of similar responses evoking unnatural synergies in which, for instance, the hand would move away from the opening mouth or the mouth would close while the hand is approaching. Also, one would expect high intensity stimulations to systematically evoke motor responses at different joints and limbs. None of these predictions is verified: first, sites evoking focal and complex movements intermingle in the precentral gyrus, which suggests that local and distributed motor representations co-exist in this region [41, 42]; second, unnatural uncoordinated synergies have not been observed in response to electrical stimulations that evoke natural coordinated responses [10]. Note that this ability of electrically stimulated responses to closely mimic the characteristics of endogenous movements has also been documented for various regions of the saccadic and gaze orienting systems [43].

At a more general level, the idea that DES produces local effects is also supported by studies in which this technique was paired with single-cell recordings [44, 45], pharmacological inactivations [45, 46] or anatomical lesions [4, 47-49]. For instance, in his pioneering work, Ferrier himself reported that stimulation and lesions of a given precentral area affected the exact same muscles [4]. Further experiments confirmed this result by showing that a lesion of a precentral area identified as the "hand knob" on the basis of electrical stimulation, resulted in a severe, localized, impairment of manual dexterity [47, 48]. Additional studies confirmed this local action of DES for other brain regions. In PMC, for instance, it was demonstrated that the neurons triggering limb movements when electrically stimulated are the same as the neurons

activated during natural goal-directed reaches [44]. Likewise, in the cerebellum it was found, using focal anatomical lesions, that movements evoked by stimulation of the cortex [7] or output nuclei [50] of this structure were not mediated by the heavy projections from the cerebellum to M1 [51], but by descending cerebello-spinal pathways going through the reticular formation [49].

Overall, all these results show that electrical stimulation of motor areas has astonishingly specific and local effects that closely mimic the characteristics of endogenous responses. Formally, the hypothesis that DES-evoked movements reflect a tetanic activation of the spinal interneurons [12] or the anarchical recruitment of some remote corticospinal projections [14], cannot be rejected. Pragmatically, however, this widely-spread criticism is clearly not supported by the experimental evidence.

DES and cognitive functions

While most authors agree that DES is a unique tool for identifying causal links between neural processes and specific cognitive functions [29, 43, 52-54], detractors of this technique assert that the propensity of electrical current to spread in a random, unpredictable manner within brain networks precludes any possibility of causal reasoning [13, 14]. This criticism is mainly based on the claim that stimulation outcomes are dramatically variable and heterogeneous. In support of this view, it is argued that DES at one site can sometimes generate opposite results while DES at distinct sites can sometimes have identical effects [14]. Although these arguments need to be carefully considered, it does not seem that the examples put forward to support them are totally fair and convincing (Boxes 1 and 2). In fact, a general evaluation of the literature seems to show the contrary, namely that electrical stimulation has, in general, highly specific and (based on data gathered from other methods) predictable effects on non-motor functions. For

instance, in human patients, conscious desires to act, formulated as general action categories ("move the arm"), have only been reported in response to stimulations of neural populations linked to movement intention in the inferior parietal lobule [6, 15]. By contrast, irrepressible impulses to act, expressed as finely characterized movements ("urge to lift right elbow" or "move right arm away"), have only been observed following stimulation of the SMA [18]. Likewise, in subjects with subdural electrodes in the inferior temporal gyrus, deficits in face perception have been shown to occur only in response to electrical stimulation of the exact neural populations that are involved in the process of facial recognition [55]. A similar observation was reported for motion detection in the medial temporal area (MT) [29, 43, 54]. The production of language offers another example of this high level of specificity. Dense connections are known to exist between frontal and temporal language-related regions [56, 57]. However only frontal areas disrupt speech when stimulated, while, on the other hand, only stimulation of temporal structures consistently causes alexia [58]. The same type of dissociation has been reported for the production of saccadic sequences. While strong interconnections link the supplementary (SEF) and frontal (FEF) eye fields, only the former region biases the order in which animals perform memorized saccades [59], an outcome that agrees with the results of single-cell recordings [60]. As shown in recent reviews [29, 43, 54], such results, which cannot be exhaustively reviewed here, are not epiphenomena. They fairly illustrate the general reality of the scientific literature on electrical stimulation, which shows that, in most cases, the behavioral effects of DES reflect disruption of neural activity at the stimulated site (see also [29]).

Of course, it may happen that roughly comparable behavioral deficits are evoked through stimulations of different areas. However, this does not necessarily mean that current anarchically spreads from the stimulated regions to a remote area that would subserve the observed behavior

[14]. The existence of multiple disruptive sites for a given function may just reflect the fact that complex cognitive responses are rarely mediated by a single brain area. Disrupting any region within a functional network is expected to prevent the correct expression of the overt behavior mediated by this network. For instance, face recognition is known to involve a distributed set of interconnected areas [61]. Consequently, it is not surprising that stimulation at different sites within this network (but not outside) disrupt face recognition [55].

It may also happen that behavioral deficits occur following electrical stimulation but not ablation of a given region. This is not surprising, considering that the brain is a highly plastic structure with high redundancy and can radically rearrange its organization in response to injuries [62]. The basal temporal language area (BTLA) is an interesting example. Stimulation, but not resection of this region has been reported to produce aphasic symptoms [63], which has been said to constitute a direct proof that DES can operate remotely through generating neural perturbations at distant sites [14]. However, neuroimaging data have linked BTLA to language processing [64] and some studies have described transient aphasic symptoms in some patients following spontaneous seizures [65] or ablation [66, 67] of this region. It is therefore plausible that the absence of long-term clinical effects when BTLA is resected echoes the existence of postoperative plastic adaptations rather than the artifactual nature of the deficits observed in response to DES. In agreement with this hypothesis, the literature provides a few other examples showing that resecting or inactivating an eloquent brain region can have little functional impact. For instance, it is now well established that ablation of the FEF induces only minor changes in saccade metrics, although electrical stimulation of this oculomotor region that projects to the brainstem oculomotor nuclei evoke saccades that resemble endogenous saccades [43]. In the same vein, resection of the SMA, a major motor area that projects to the spinal cord and triggers

movements when stimulated (see above), results in severe but highly transient behavioral deficits [68, 69]. Even, Broca's area, a region that clearly perturbs language production when stimulated [58], can be removed in some patients without inducing permanent language deficits [62].

Still, the data above do not mean that remote effects never drive DES outcomes. However, even in this case, the evoked behaviors are unlikely to reflect an aberrant, meaningless jumble of current spread. Convincing evidence exists that DES propagates within physiological pathways in a way that mimics the neural recruitment observed in natural situations [29, 52]. In V1, for instance, DES generates activity in specific, topographically related sites of the extrastriate cortex [70]. Likewise, in the ventral visual pathway, stimulation of a given point within the neural network mediating face recognition produce activations in a restricted set of regions containing face-selective neurons [61] (Figure 2). So, at worst, it may be said that DES allows to map anatomical nodes within structured functional networks. From an interpretative perspective, such a conservative claim does not challenge the view that DES exerts a causal action on the observed behavior (see also [29]).

In practice, these data raise the question how to distinguish between direct and remote effects of DES. Although there is no perfect way to do so, a powerful approach, illustrated in several examples above, is to combine DES results with observations from others experimental techniques, including neuroimaging, anatomical tracers, single-cell recordings, pharmacological inactivation studies, and anatomical lesions. It should be clear that DES outcomes cannot be unambiguously interpreted in isolation. However, this should not be used to dismiss DES observations as uninterpretable *a priori*. For instance, in awake patients, electrical stimulation delivered over the inferior parietal lobe triggers feelings of conscious intention [6]. Numerous data from various fields link this region to the emergence of conscious motor intention [71, 72].

So, the conclusion that DES has a direct causal effect on the observed behavior seems far more plausible than the ritualistic standpoint that the effect is mediated by another, so far unknown, brain structure [13]. A revealing example of how data from various fields can help distinguishing between direct and remote effects of DES can be found in studies describing the occurrence of organized defensive movements after stimulation of the ventral intraparietal area (VIP) in monkeys [73]. Because VIP has no direct access to motoneurons, these defensive movements have to be mediated by some remote region. Interestingly, VIP is monosynaptically connected with a precentral area (PZ) that projects to motoneurons and evokes similar defensive responses when stimulated [10]. As a consequence, the most plausible hypothesis would be that DES over VIP triggers sensory signals that are conveyed to PZ, where they activate neural representations of defensive behaviors which, in turn, recruit descending projections associated with the expression of these behaviors [74, 75]. In this example however, movement does not result from a blind artificial spread of current in some distant area, but from the recruitment of an organized functional circuit that supports the production of endogenous defensive actions. Inactivating PZ while stimulating VIP would make it possible to directly test this hypothesis.

DES and clinical mapping

Probably the most direct and convincing evidence that DES has specific, highly reliable effects comes from the successful use of this technique during functional peri-operative mapping in human patients with brain tumors. Since the pioneering work of Penfield, DES has proved highly efficient for identifying eloquent regions related to motor and cognitive functions [5, 53, 76, 77], which allows to dramatically reduce the occurrence of permanent postoperative sequelae in the patients while significantly improving their long-term survival [78-80]. Regarding

language, for instance, partial resection of neural sites identified as eloquent by DES gives rise to permanent deficits [81]. By contrast, preservation of these sites allows complete recovery of linguistic functions within 6 months, in almost 99 % of the subjects [58]. As shown by a recent study, although preoperative neuroimaging techniques can be helpful for guiding the surgical act, they are, by far, not as effective as DES for ensuring a safe and complete ablation of the tumor [82].

In light of these results, DES critics have recently suggested that a conceptual boundary should be drawn between the clinical and fundamental merits of DES [14]. While this technique would be valid for causally identifying eloquent regions in surgical setups, it would represent an equivocal and unreliable approach for studying brain functions in fundamental contexts. The reason for such a conceptual segregation seems quite obscure. If, as claimed with respect to fundamental neuroscience, DES effects are so unreliable and reflective of an artificial spread of current at local and distant sites, then we must ask how it can be that this technique is so effective at preventing postoperative deficits in neurosurgical contexts. In other words, if the result of stimulating a given area cannot tell us anything about the functional role of this area, then one should expect DES to have no significant clinical benefits. Clearly, this is not what the literature demonstrates. The clinical effectiveness of DES is highly consistent with one of the key hypotheses of the present paper, namely that this technique offers critical insights into brain functions.

Concluding remarks

To summarize, it appears that, during the last century, DES has provided a unique body of knowledge about the anatomo-functional organization of the brain [29, 43, 52-54, 58].

However, despite this extremely valuable contribution, the same criticisms keep appearing in the literature to challenge the relevance and reliability of DES results (Box 3). The evidence reviewed in this paper show that these ritualistic, knee-jerk criticisms are no longer tenable when the actual scientific literature on DES is considered. The view that current delivered at a given brain site spreads in a meaningless jumble cannot be reconciled with the striking specificity of DES outcomes and the fact that electrical stimulation dramatically minimizes post-operative deficits during brain surgery. From a functional point of view, the body of knowledge provided by converging experimental approaches allows, in most cases, to convincingly interpret DES outcomes and distinguish between local and remote influences.

Like any other neuroscientific technique, DES is certainly not flawless. However, it is also not as indecisive and equivocal as it is sometimes said to be on the basis of purely theoretical considerations. It is our belief that actual data should be given more credibility than conceptual constructs when evaluating the merits of any experimental approach.

Box 1: Can DES at one site give rise to opposite behavioral effects?

A major argument against the specificity of DES states that stimulating a given site with different parameters (frequency, duration) can generate contradictory behavioral outcomes [14]. Although attractive at first glance, this argument may not be as strong as it seems. Indeed, strictly speaking, opposite behaviors are not observed "at the same site". At best, they are found within the same broad region, generally in different subjects. To make this point clear, let us evaluate the evidence put forward by Borchers et al. [14] to support this claim that opposite effects can be evoked from a given cortical site (Figure Box 1). In this review, the authors consider several examples such as vocalization and inability to speak, conscious motor intention and anomia, and paresthesia and numbness. It is explicit from Penfield's pioneering work (which is cited by the authors of the review) that vocalization and inability to speak are not found at the same locations [5]. Also, to the best of our knowledge, no evidence is available, to date, that a single neural site can evoke conscious motor intentions while also causing anomia (a possibility that was directly investigated by Desmurget et al. [6]). Finally, it is unclear why paresthesia would be a positive behavioral sign while numbness would be a negative one. Classically, numbness is considered a manifestation of paresthesia. Penfield himself (whose data are used by the authors of the review) makes it clear that numbness and other type of sensations (in particular tingling) cannot be segregated from his study [5]. According to this author "*in 204 responses [the quality of sensation resulting from cortical stimulation] was called tingling or electricity, 131 times numbness, which at times was explained to mean numbness with tingling, at other times absence of all sensation*" ([5], p 433). One patient, for instance, reported a sensation in the hand and finger, "*when asked what the sensation was like she replied: 'like going to sleep.' When asked if it was numbness or tingling, she replied "Both'* " ([5], p 400). In light of these results, it

seems that a fair account of the existing literature would not state that DES at one site can have opposite behavioral effects, but rather that broad cortical regions can be involved in more than just one cognitive or motor function.

Box 2: Does DES at different sites evoke similar behavioral effects?

Another major argument against the specificity of DES states that stimulating distant areas can evoke identical behavioral outcomes [14]. This is a puzzling claim for at least two reasons. First, most motor and cognitive functions does not rely on the recruitment of a single brain region but rather on the recruitment of distributed networks of distant areas. So, it does not seem unreasonable at all to assume that the stimulation of distant regions may affect the same general behavior [83]. Second, studies reporting that DES delivered at distant sites has similar effects do not seem common in the literature, especially in the cognitive domain. As a matter of fact, we were unable to find a totally convincing example in which DES would evoke strictly identical cognitive outcomes for stimulations delivered over different brain regions. To illustrate this point let us consider the evidence that is said to contradict this assertion in the review of Borchers and colleagues [14] (Figure Box 2). According to these authors, three areas evoke an identical "desire to move" when electrically stimulated: the inferior parietal lobule (IPL), the supplementary motor area (SMA), the precentral gyrus (PG). Technically, this claim of similarity cannot be evaluated for PG since Penfield did not provide any precise information regarding the sensation experienced by his subjects for this site [5]. What about SMA and IPL? In the former region, the patients typically report a compulsive desire to act with no sense of agency [18]. The movements are described in very accurate terms (e.g. an "urge to move right leg inward") and when the intensity of the current is increased, a motor response actually occurs. IPL stimulation

provides a very different picture in which the patients report their motor intentions in very general terms with a strong sense of agency [6]. When prompted to describe the exact movement they wanted to execute, they either say that they "don't know" or they only provide a vague description evoking, for instance, "a desire to move the hand". No movement is ever evoked at these sites even at high intensities. Together, these data indicate that the effects of stimulating IPL and SMA are not similar at all. The contrasting responses observed for these regions are consistent with the conclusion that intentions in IPL are related to the early selection of a motor response not yet constructed, whereas the urge to move found in SMA is related to the late imminent release of an already planned movement [6, 72].

Box 3: Outstanding Questions

●) Is Direct Electrical Stimulation (DES) an "uncontrollable", "poorly understood" technique?

●) Does DES spread blindly within cerebral networks?

●) Does DES evoke variable (sometimes opposite) effects at the same cortical site?

●) Does DES evoke identical effects at distant cortical sites?

●) If DES if so unreliable how can we explain its remarkable ability to minimize postoperative deficits in brain damaged patients?

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Figure 1: Functional and spatial specificity of the DES-evoked movements. Left panels show: (A) EMG signals related to a multijoint movement typically evoked by stimulating the precentral sulcus -flexion of the left wrist, fingers, and elbow, as well as a rotation of the forearm- (individual brain of the patient; blue area represents the premotor cortex; adapted from [6]. (B) EMG signals related to a focal single-joint response typically evoked by stimulating the cerebellar cortex in patients with extracebellar tumors -flexion/abduction of the thumb- (individual cerebellum of the patient; bright area represents the surgical bone flap; adapted from [7]). Right panels display maps of complex movements in the precentral gyrus (adapted from [35]). (C) Simulations at various sites in the precentral gyrus cause the hand to move to different spatial locations (the shaded region displays the cortex normally buried in the anterior bank of the central sulcus); (D) Subregions displaying specific functional properties within the general map of hand positions. T, tumor; DE, deltoid; TR, triceps; BI, biceps; FDS, flexor digitorium superficialis; EDC, extensor digitorium communis; ADM, abductor digiti minimi; FDI, first dorsal interosseous; OP, opponens pollicis; THE, Thenar.

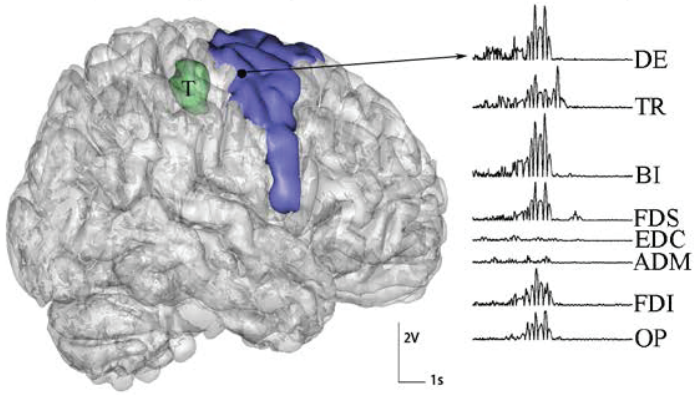
Figure 2: Illustration, for an individual monkey, of the selective propagation of DES within meaningful physiological pathways. (A) Face-related areas are identified by fMRI (regions more activated by faces than by other objects) and reported on the flattened cortical surfaces for the right hemisphere. (B) Areas significantly activated by stimulating the site 'x' within area ML. For the sake of legibility, face-related areas identified with fMRI (left panel) are indicated by the green outlines. Anatomical labels: IPS, intraparietal sulcus; SF, Sylvan fissure; STS, superior temporal sulcus; LS, lunate sulcus; IOS, inferior occipital sulcus; and OTS, occipitotemporal sulcus. Designation of face-selective areas: “PL,” posterior lateral; “MF,” middle fundus; “ML,”

middle lateral; “AF,” anterior fundus; “AL,” anterior lateral; “AM,” anterior medial. Adapted from [61].

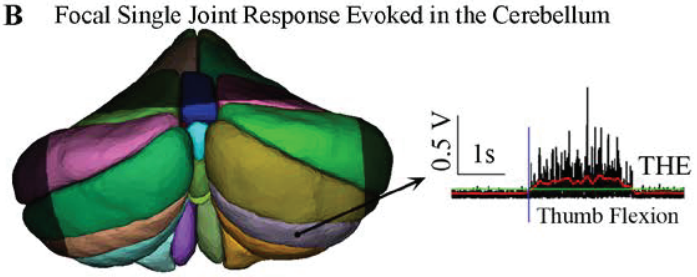
Figure Box 1: It is argued that opposite behavioral outcomes can be evoked by stimulating the same cortical site (panel A adapted from [14]). This assertion seems questionable as illustrated in two examples. First, the actual data from Penfield and Boldrey show clearly that the "inability to speak" and "vocalization" behaviors are mostly evoked in the same broad precentral region but at different sites and generally in different subjects (panel B adapted from [5]). Second, direct comparison between the sites evoking "anomia" (panel C adapted from [77]) and "conscious motor intention" (panel D adapted from [6]) shows some degree of anatomical overlap. However, this overlap does not seem to warrant the strong conclusion that the "same sites" are involved. Blue triangles in panel D represent sites that were positive for motor intention but negative for anomia in one subject with a left side tumor.

Figure Box 2: It is argued that identical behavioral outcomes can be evoked by electrical stimulation from distant cortical site (panel A adapted from [14]). A close inspection of the actual data does not seem to support this view. Panels B (adapted from [6]) and C (adapted from [18]}) show typical verbatim reported by subjects stimulated respectively in the inferior parietal lobule (IPL) and supplementary motor area (SMA) (verbatim were not available for the precentral site). While IPL stimulation evokes general desires to move with a high sense of agency, SMA stimulation evokes urges to perform highly specific movements. When the intensity of the stimulation is increased movements occur in SMA but not IPL.

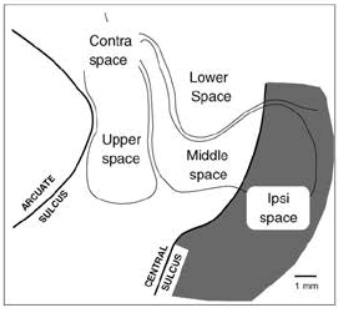
A Complex Multijoint Response Evoked in the Precentral Gyrus



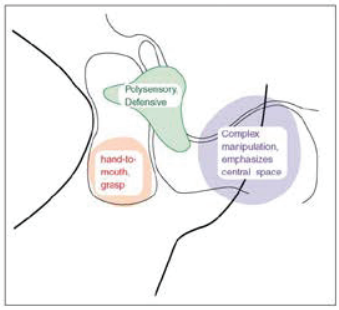
B Focal Single Joint Response Evoked in the Cerebellum

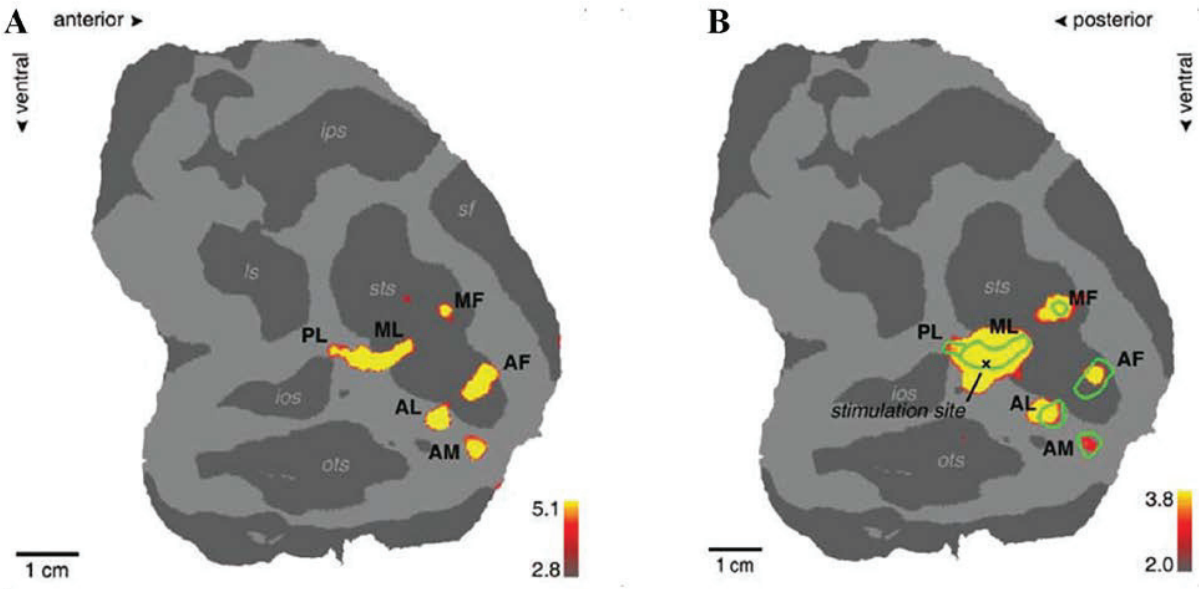


C Map of Evoked Hand Position



D Specialized Subregions

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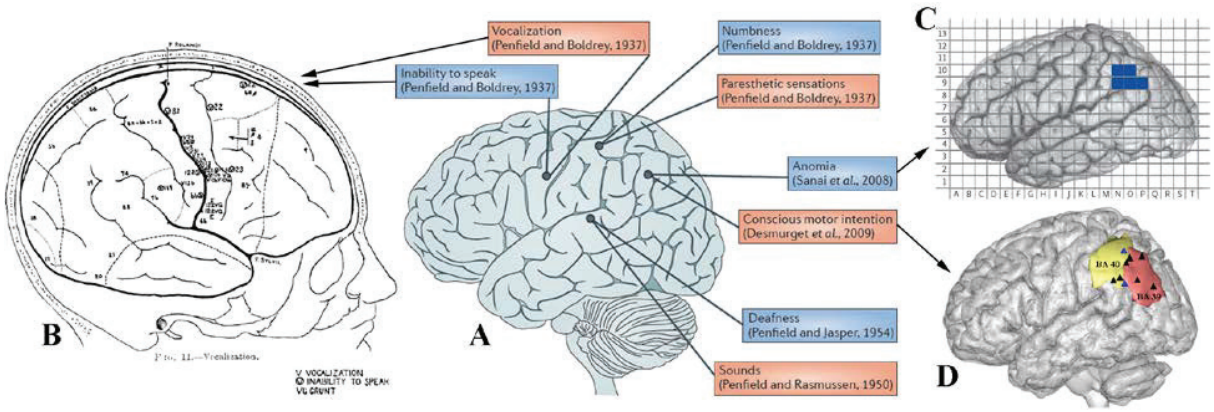
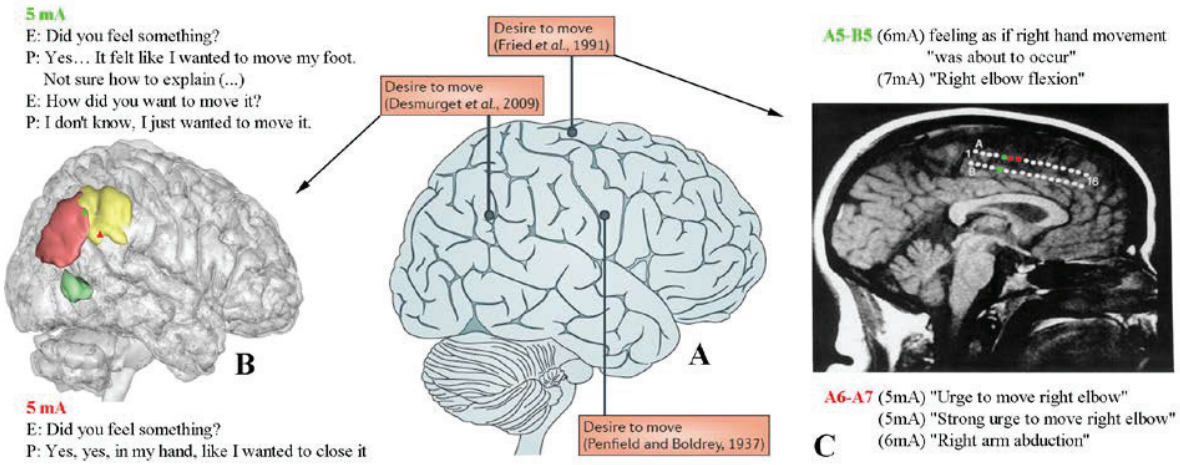

Vocalization
(Penfield and Boldrey, 1937)
Inability to speak
(Penfield and Boldrey, 1937)
Numbness
(Penfield and Boldrey, 1937)
Paresthetic sensations
(Penfield and Boldrey, 1937)
Anomia
(Sanai et al., 2008)
Conscious motor intention
(Desmurget et al., 2009)
Deafness
(Penfield and Jasper, 1954)
Sounds
(Penfield and Rasmussen, 1950)
A
B
C
D
BA 40
BA 39


5 mA
E: Did you feel something?
P: Yes… It felt like I wanted to move my foot.
Not sure how to explain (...)
E: How did you want to move it?
P: I don't know, I just wanted to move it.
Desire to move
(Fried et al., 1991)
Desire to move
(Desmurget et al., 2009)
A5-B5 (6mA) feeling as if right hand movement
"was about to occur"
(7mA) "Right elbow flexion"
B
A
5 mA
E: Did you feel something?
P: Yes, yes, in my hand, like I wanted to close it
Desire to move
(Penfield and Boldrey, 1937)
A6-A7 (5mA) "Urge to move right elbow"
(5mA) "Strong urge to move right elbow"
(6mA) "Right arm abduction"
C

II.3 Study 3- Motor intention and movement preparation

Article II

Conscious Intention Is Not An Emergent Outcome Of Motor Preparation

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Abstract

Since Libet seminal observations, it is often assumed that conscious intention emerges during motor preparation, when neural activity reaches a sufficient threshold. If this hypothesis is valid, the time required to prepare a movement should be longer than the time elapsing between the emergence of conscious intention and the onset of this particular movement. To investigate this prediction we measured, in the same subjects: (1) the time of movement onset with respect to the time of emergence of conscious intention ($RT_{/int}$) using Libet's original press-button paradigm; (2) the time of movement onset with respect to the appearance of a visual stimuli ($RT_{/ext}$) using the same press-button task. Results indicate that $RT_{/int}$ (273 ms) was close and not statistically different from $RT_{/ext}$ (264 ms). This statistical identity is not consistent with the widespread idea that conscious intention emerges progressively during motor preparation.

Key words: motor intention, conscious intention, motor reaction time, motor preparation, Libet task.[1]

[A]bbreviations. $RT_{/int}$: internal reaction time, defined as the duration between the time of conscious intention and movement onset; $RT_{/ext}$: external reaction time, defined as duration between presentation of the visual stimuli and movement onset; WT: time of emergence of a will to move with respect to movement onset in Libet paradigm (= $-RT_{/int}$); MT: duration between the estimated and actual times of movement; RP: Readiness Potential; EOG: Electrooculography; IPL: Inferior Parietal Lobule; SMA: Supplementary Motor Area.

1. Introduction

Does motor preparation lead to conscious intention? The debate on this issue has been vivid since the pioneering experiment of Libet and his colleagues. In this work, human subjects kept watching a clock and reported the time when they felt a 'will to move' (W-judgment Time; WT) [26]. Two main findings were reported. First, WT occurred approximately 250 milliseconds prior movement onset. Second, an early marker of motor preparation, the readiness potential (RP), emerged around 1 second before the time of button press. Since their publication, these results have been widely replicated [13, 19, 32] and interpreted in reference to the idea that conscious intention is an emergent outcome of motor preparation (for reviews [17, 18]). According to this view, *"the brain begins the preparation to move prior to the conscious appreciation that this is happening, and the sense of volition gradually develops in conscious awareness thereafter"* [29]. However, an alternative hypothesis was recently put forward in which it was claimed that the existence of an early brain activity did not reflect motor preparation per se, but rather the buildup of the neural signal that leads to the emergence of conscious intention [13]. Within this framework, actual movement preparation does not precede but follow the conscious decision to act [6, 8, 13]. Recently, these views were both challenged by a third hypothesis according to which the neural activity that precedes the time of conscious intention reflects spontaneous neural fluctuations which could bias the decision to move but is not the pre-conscious process of making intentional decision [30].

Although disentangling, the different hypothesis above is not simple, it has been argued that directly comparing WT with the motor reaction time observed in response to an external stimuli ($RT_{/ext}$) might be of interest [5, 8]. Indeed, $RT_{/ext}$ reflects the time between cue onset and movement onset and this variable is commonly thought to indicate the duration of motor preparation. As a consequence, if conscious intention emerges during motor preparation, then for a given movement, $RT_{/ext}$ should be significantly longer than the time elapsing between the emergence of conscious intention and the onset of the movement. Thereafter, this time is designated $RT_{/int}$ ($RT_{/int}$ is positive and equal to -WT; it can be readily compared to $RT_{/ext}$).

Based on the existing literature, it can be observed that $RT_{/int}$ and $RT_{/ext}$ are generally of similar magnitude [5, 8]. However, to be trustworthy, the comparison between these two measures needs to be performed in the same subjects under similar experimental conditions.

Indeed, due to variations in subjects' samples and/or in experimental conditions, highly variable values have been reported from study-to-study in the literature for $RT_{/ext}$ and $RT_{/int}$. Regarding $RT_{/int}$, for instance, the mean value, averaged across subjects, was reported to be 204 ms by Libet et al. [26], 240 ms by Sirigu et al. [32], and 355 ms by Haggard et al. [19]. For $RT_{/ext}$ even larger changes were found, with mean variation ranging from 170ms [34] to 450ms[23].

In this study, we instructed the same subjects to perform a strictly identical press button task in two randomly ordered conditions: (1) Libet's condition in which $RT_{/int}$ was measured; (2) A visually-triggered condition in which $RT_{/ext}$ was measured. Using the same motor task in both conditions was important to ensure that potential differences in RT values were not related to disparities in the processes of motor planning. Indeed, in this behavioral experiment, our goal was to determine whether $RT_{/ext}$ is significantly longer than $RT_{/int}$, as is predicted by the classical idea that conscious intention emerges from the process of motor preparation [5].

2. Methods

2.1 Participants

Twenty-one right-handed subjects (19-31 years old, 13 women) with normal- or corrected-to-normal vision participated in the experiment. The protocol was approved by the local ethical committee and all subjects gave their informed consent prior to the experiment.

2.2 Apparatus and Procedures

In the first task, we reproduced Libet's original protocol [26]. In brief, subjects were comfortably seated in front of a computer screen. In their right hand, they held a small button to be pressed with the right thumb (Fig. 1A). Each trial involved 4 steps (Fig. 1B-G): (1) an analog clock appeared on the screen with the clock's hand starting to rotate immediately from a randomly selected location; (2) subjects were instructed to wait, at least, for one complete rotation of the clock's hand, before pressing the button as quickly and as abruptly as possible when they first felt a desire to do so; (3) before stopping, the clock kept rotating for a randomly selected duration of 800 to 2100ms; (4) An instruction screen was then presented instructing the subjects to report

either the time when they pressed the button or the time when they had the “intention” to press the button. To allow direct comparison with the reaction time data collected in the visually triggered press button-task (RT/ext, see below), we defined reaction time for Libet task as the duration between the time of conscious intention and movement onset (RT/int; Fig. 1). RT/int is the opposite of the WT variable typically used by Libet and his followers. The same approach was used to define the estimated instant of key press (MT): MT represents the duration between the estimated and actual instants of key-press (Fig. 1). The conditions of estimated key press or conscious intention were presented in two independent blocks of 60 trials each, and randomly counterbalanced across subjects. Each complete rotation period of the clock's hand lasted 3000ms. The clock figured 60 time point intervals each corresponding to a 50 ms increment.

The second task was a simple visual reaction time task. A schematic representation of the experimental apparatus is presented in Fig. 2. Subjects were comfortably seated in front of a horizontal circular array of light emitting diodes. As in the previous task, they held a small button to be pressed with the right thumb. The center diode was used as the fixation point. The other diodes (n = 24) were used as visual cues. They were positioned around 3 circles centered on the fixation point. The circles had different radii of 4, 8 and 12 cm. Cues were positioned at 0, 45, 90, 135, 180, 225, 270 and 315 degree with respect to the sagittal direction. The fixation diode was illuminated at the onset of the trial and maintained on until its completion. After a delay, randomly chosen within a range of 1 to 2 s, one of the visual diodes was pseudo randomly selected and turned on. Each target was presented 5 times, leading to a total of 120 trials. Randomization of target locations and time to stimulus onset was used to minimize the risk of motor anticipation. RT/ext was defined as the time between stimulus onset and key-press. The subjects were instructed to keep visual fixation throughout the trial and to press the button as quickly as possible in response to the visual cue. In this task, eye movements were monitored on-line using electrooculography (EOG) at a sampling frequency of 1000 Hz [9]. EOG signal was displayed on a control screen at the end of the trial. 3.6% of the trials were discarded on-line and presented again later in the session because the subjects broke eye fixation or were holding the press button down at the appearance of the fixation cue.

2.3 Data analysis

In both conditions, further off-line analyses were performed to identify erroneous RT values. For Libet's task, the trials in which subjects pressed the button before one full rotation of the clock's hand were discarded (estimated key-press trials: 3.1%; estimated conscious intention trials: 3.5%). For the visual reaction time task, trials with aberrantly short (< 100 ms) or long (> 1000 ms) RT were discarded from data analysis. Also, for each subject, outliers with values above or below 3 standard deviations of the mean were removed. Applying these criteria led to a rejection rate of less than 2 %. Mean $RT_{/int}$, $RT_{/ext}$ and MT were determined from the valid trials. With respect to this point, it may be worth noting that statistical results were not affected when analyses were performed without rejecting any trial or using slightly different rejection criteria (e.g. 2 SD instead of 3 SD or 150 ms for identifiying anticipated responses instead of 100 ms).

Because Levene's test for heterodasticity of variance between groups was significant ($p < .005$)[31], the non-parametric Friedman ANOVA (one-way repeated measures ANOVA on ranks) [14] was used to identify significant differences between the experimental conditions. The Wilcoxon rank test [36] was then used for post-hoc comparisons. Because 3 comparisons were planned, the statistical threshold ($p < .05$) was corrected for multiple comparisons using Bonferroni procedure (corrected $p = .017$)[37]. The Wilcoxon rank test was also used to test whether MT was significantly different from the time of movement onset (i.e. significantly different from zero).

3. Results

In agreement with the results of previous studies [13, 19, 32], our subjects exhibited a good ability to estimate movement onset. The instant of button press occurred slightly after the instant estimated by the subjects (MT = 43 ±61 ms), which indicates that the participants were able to use the clock's hand accurately to estimate time events (Fig. 3). Still, MT was significantly different from zero (Wilcoxon, $z= 2.7$, $p < .01$), showing that the subjects slightly

anticipated the actual time of button press. This anticipation might reflect, at least for a part, conduction delays and muscle inertia.

Regarding intention to move, the subjects reported that their decision to act occurred 273 ms (±129) before movement onset, which agrees with the results of prior studies [13, 19, 32]. This value is remarkably close to the 264 ms (±33) reaction time found in the visual task condition. Statistical analysis revealed the existence of a significant difference between the 3 experimental conditions (Friedman ANOVA, $F= 32$, $p < .0001$) (Figure 3). Post-hoc comparisons indicated that $RT_{/ext}$ and $RT_{/int}$ were significantly different from MT (Wilcoxon Rank test, $z > 4.0$, $p < .0001$) but not from each other (Wilcoxon Rank test, $z > 0.71$, $p > .45$).

Additional analyses were conducted at the individual level under the assumption that if motor preparation leads to the emergence of conscious intention, $RT_{/ext}$ should be longer than $RT_{/int}$ in most (if not all) subjects. Results indicated that this was not the case. In fact, more than half of the subjects (12 / 21) exhibited longer $RT_{/int}$ than $RT_{/ext}$.

In a last analysis, we tried to correlate $RT_{/int}$ and $RT_{/ext}$ assuming that if motor preparation starts after cue onset (whether internal or external), one may observe a tendency for the subjects who need more time to initiate their movement, to do so in both conditions. Correlation failed to reach statistical significance (Spearman's rho = 0.11, $p > .60$). This inability to reject the null hypothesis is not totally surprising given the existence of a high variability in the estimation of $RT_{/int}$. To evaluate this claim we performed a power analyses using the spearman's rho value found in our sample and a power of 90 % (Statistica 8.0®). Results indicated that a sample of more than 460 subjects would be required to reject the null hypothesis.

4. Discussion

Our data show that there is no significant difference, on average, between the time required to initiate a movement in response to a visual cue ($RT_{/ext}$) and the time required to initiate the same movement in response to an internal intention to act ($RT_{/int}$). This observation does not support the claim that conscious intention to act emerges in response to the neural activity mediating motor preparation [17, 20, 29]. Although our data could be compatible with

the alternative view that a conscious intention to act triggers motor preparation, at least in the context of Libet's protocol [5, 8, 13], they do not directly support this idea. It could be, for instance that these two processes are largely parallel, as could be suggested by the theory of distinct pathways for perception and action [4, 15]. With respect to this point, one should acknowledge that our inability to identify a significant difference between $RT_{/int}$ and $RT_{/ext}$ could reflect a lack of statistical power [28]. However, even if this is the case, the magnitude of the difference we observed between RTs seems too small (9 ms) to be compatible with the results of EEG studies suggesting that RP (considered as a marker of motor preparation) precedes the emergence of motor preparation by several hundreds of milliseconds [19, 26].

The absence of a causal link from motor preparation to conscious intention is consistent with a recent study showing that motor intentions can arise independently of motor preparation in humans [7]. Following electrical stimulation of the inferior parietal lobule (IPL) during awake brain surgeries (BA 39-40), patients report conscious intentions to move or talk. These intentions are formulated in very broad and general terms ("a will to move the chest" or "a desire to move the foot") and the patients do not spontaneously describe the exact movement they want to perform. When prompted to do so, they report that they "don't know" which, clearly, would not be expected in a conceptual framework where movement intention results from the unconscious neural processes mediating the planning of a specific motor response. Strikingly, such an accurate description of the movement to be performed arises in response to sub-motor-threshold stimulations of the supplementary motor area (SMA)[12]. In this case, the subjects report compulsive urges to move "the right leg inward" or "the right thumb and index finger". In contrast to what is observed following parietal stimulations, when the intensity of the stimulation is slightly increased, the intended movement actually occurs. In light of these observations, it has been suggested that conscious intentions in IPL are related to the initial selection of a motor response not yet planned, whereas the urges to move in SMA are associated with the release of inhibition that occurs in this region when the intended movement has been planned and is ready to be performed [2, 7, 8].

These data seem consistent with recent observations that challenge Libet's original assumption that the readiness potential (RP) is an early marker of motor preparation [5, 8, 13, 16]. Anatomically, the medial prefrontal region, and more precisely the SMA, is thought to be

the main source of RP [11, 22]. In patients with lesions of IPL, the motor part of Libet's task (i.e. pressing the button and estimating the time of button press) is correctly executed although no RP is observed [32]. In the same way, in healthy humans, RP has been associated with the process of paying attention to the timing of movement [1] or the rotating clock [27]. It emerges whether the subjects plan a movement or not [21, 33]. This latter observation seems in line with recent computational data indicating that the gradual buildup of RP prior to initiation of self-initiated movements could be mostly artifactual and related to flucutations of neural activity [24, 29].

At a more "philosophical" level, it has been suggested that free will is a mere illusion because we only become aware of our intention to move after the desired action has already been planned in our brain [17, 18, 35]. Our data challenge this claim, at least in the context of Libet's paradigm. Indeed, we have shown that the actual implementation of a simple motor response does not precede the conscious intention of performing this action. This does not mean, of course, that unconscious processing are not involved in the emergence of a conscious intention to do something [3, 10, 25]. However, this challenges the common view that we become aware of our intention to act during the course -and as a result of- motor preparation.

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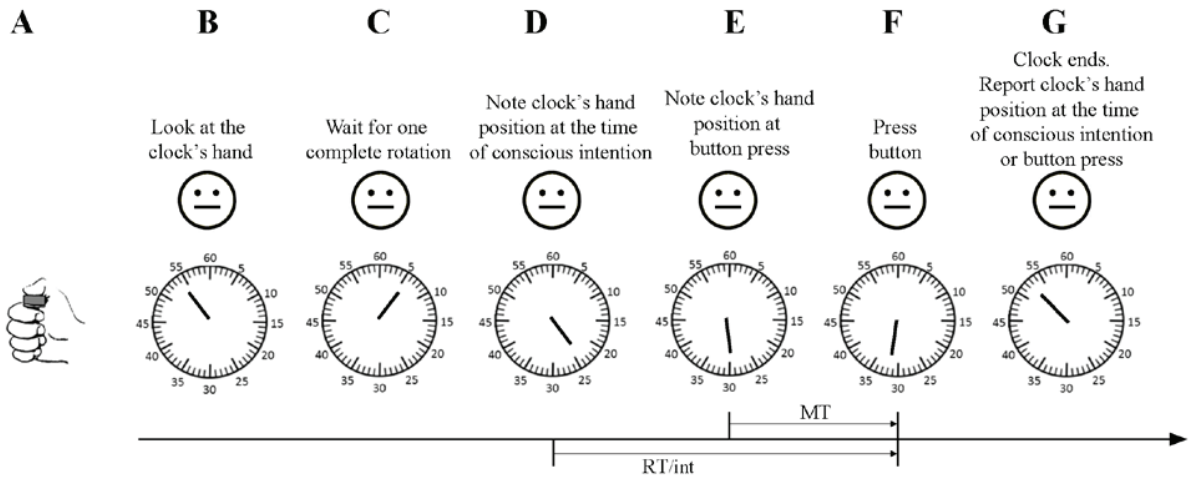
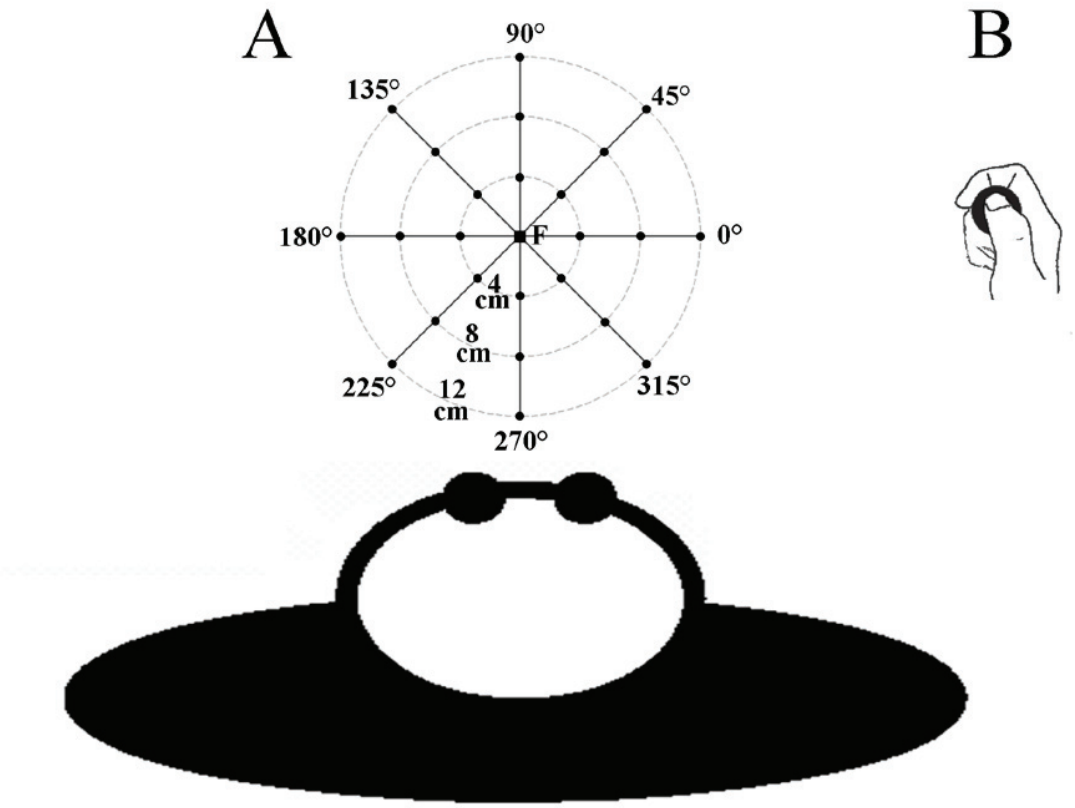
Figures

Figure 1. Schematic representation of Libet's press-button task. (A) Movement in this task is to voluntarily press a button with the right thumb. (B) The trial begins with a clock appearing in the center of a computer monitor. The clock's hand starts to rotate from a random location. (C-F) Subjects are instructed to wait for, at least, one complete rotation of the clock's hand before pressing the button as quickly and as abruptly as possible, when they first feel a desire to do so. After the movement has been performed, the clock's hand continues to rotate for a random duration ranging from 800 to 2100 ms. (G) Following the stop of the clock's hand, the subjects are asked to report, depending on the experimental condition, the time point when they pressed the button or the time when they had the "intention" to press the button. MT : movement time. $RT_{/int}$: duration between the time of conscious intention and button press.

Figure 2. Schematic representation of the experimental apparatus used for the visual task. Subjects were seated in front of the table with their gaze anchored on the central fixation diode (fixation point, F). Eye movements were not allowed. 24 light emitting diodes (blackpoints) were positioned around 3 circles (dash line) having a common center (F) but 3 different radii and 8 directions.

Figure 3. Chronometric results for each experimental condition. (< .05 indicates statistical significance of post-hoc comparison ; ns : non significant).


A
B
C
D
E
F
G
Look at the clock's hand
Wait for one complete rotation
Note clock's hand position at the time of conscious intention
Note clock's hand position at button press
Press button
Clock ends. Report clock's hand position at the time of conscious intention or button press
MT
RT/int


A
90°
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45°
180°
F
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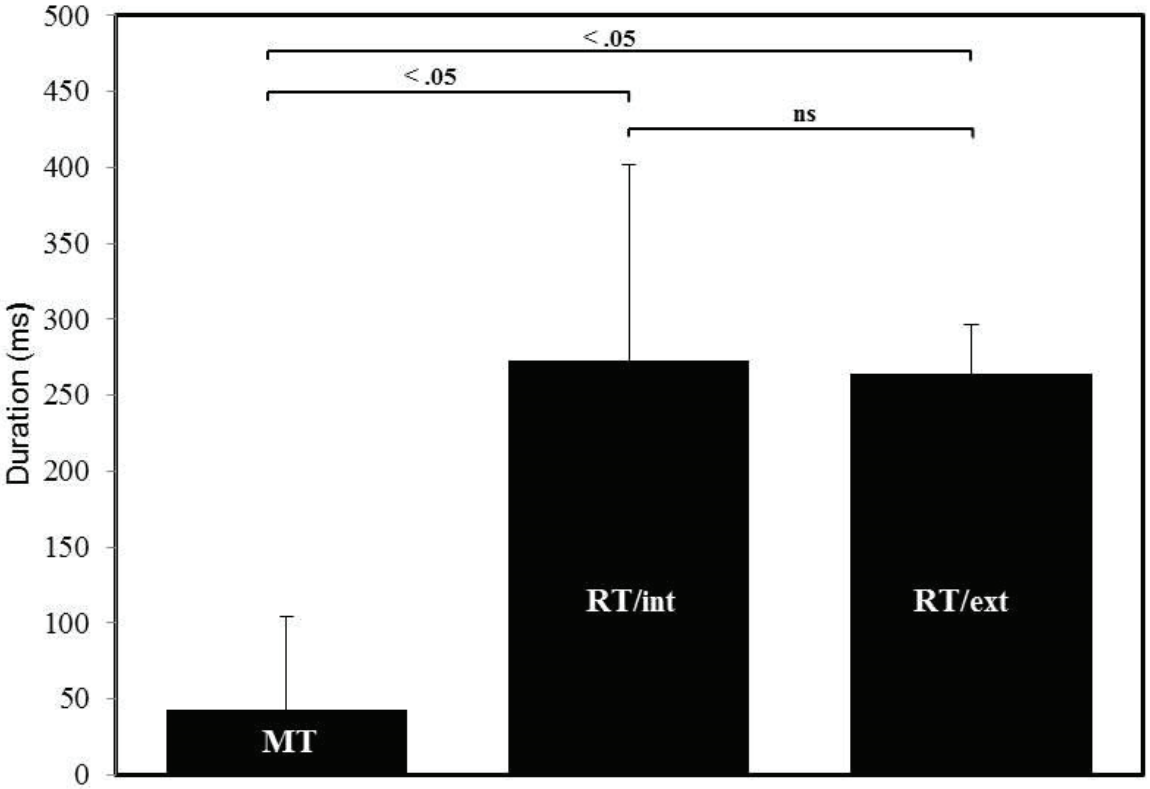
cm
8
cm
225°
12
cm
315°
270°
B


500
450
400
350
300
250
200
150
100
50
0
Duration (ms)
< .05
< .05
ns
MT
RT/int
RT/ext

Chapter III. General Discussion

The neural basis of functional organization in human sensorimotor system is not yet clear. Recent histological and physiological studies in primate shed light on this issue by indicating that motor synergy is the possible structure underlying functional organization in M1(Overduin et al., 2008; Rathelot and Strick, 2006, 2009). In human, evidence of motor synergy in M1 is also reported in stimulation study (Desmurget et al., 2014). We notice that the volume overlapping observed in fMRI study is hard to be explained as direct representation of simple movement, but in turn resembles the interleaved organization of CM cells innervating different muscles. Thus in our study, we re-examine the pattern of volume overlapping with winner-take-all procedure and we find an interleaved pattern of activation volumes within hand region.

Although in behaving monkey, the parietal cortex has been systematically mapped with sensory and motor stimuli (Hyvärinen, 1981; Rozzi et al., 2008), in human, the functional organization of simple movement hasn't been examined in detail with respect to the modern subdivisions (Scheperjans et al., 2008)(Caspers et al., 2006). In our fMRI study, we systematically examine and confirm the existence of a somatotopic map of voluntary simple movements of different body parts in the most anterior subdivisions, including area PFt, PFcm and PFop(Caspers et al., 2006). This result implies that human anterior most part of IPL could be the homologue of monkey IPL.

The emergence of conscious motor intention is related to the neural process of the posterior part of IPL (Desmurget and Sirigu, 2012; Desmurget et al., 2009; Sirigu et al., 2004). But its relationship with motor preparation is not clear (Desmurget and Sirigu, 2012). One of the hypothesis claims that motor intention emerges during the process of motor preparation, however, we confirm that for the motor task with minimum cognitive demand, for example, simple button press, the duration between the emergence of motor intention and motor output is identical with the duration between external go cue and motor output, thus denies the possibility that motor preparation starts before the emergence of motor intention.

Human sensorimotor system comprises the primary sensorimotor cortex, the secondary motor areas, cerebellum and IPL. They contribute to different aspects of human motor control and have different structures of functional organization. Further study is needed to clarify the intra-hemisphere connections of IPL with other sensorimotor brain areas, which will help us

understanding 1) the functional complexity of IPL, and 2) the different contribution of each subregions of IPL in human motor control.

III.1 Somatotopic organization in human sensorimotor system: revisited and new evidence

1. Functional organization in sensorimotor cortex

1.1 Somatotopy of simple repetitive movements in M1 and S1

In M1 and S1, with our data obtained in the first fMRI experiment, we found that although considerable volume overlapping exists between the neural representations of proximal limbs, such as fingers and elbow, the geographic centers (i.e. COG) of these activation volumes are statistically independent and organized in somatotopic manner. This observation is consistent with the findings of previous stimulation studies (Penfield and Boldrey, 1937) (Penfield, 1950) and fMRI studies (Rao et al., 1995) (Meier et al., 2008) (Beisteiner et al., 2001; Hluštík et al., 2001; Indovina and Sanes, 2001).

The somatotopy in M1 and S1 of large body parts is merely challenged in last half century, however, in fMRI studies, the extensive spatial overlapping between independent movements of different body parts implies that the basic motor unit in M1 may not be organized to serve the innervation of simple movements. An alternative hypothesis is motor synergy (Rathelot and Strick, 2006). Several observations related to this issue are also found in our experiment, and could be explained by some most recent findings in primate.

First, although the neural representations of three individual fingers overlapped more the 60% of their volume size, the overlapped regions exhibiting an interleaved pattern (**Figure 15**). Therefore, this result doesn't support the theory that the basic neural organization in M1 is in terms of single finger movement which should be arranged orderly in M1(Asanuma and Ward, 1971) (Asanuma and Rosén, 1972a), that is to say, there is no independent zone for innervating each simple finger movement. Alternatively, this observation echoes the recent findings in primate that the cortico-motoneuron (CM) cells of one digit muscle intermingle with those of another digit muscle and they all distributed widely within the hand regions **(Figure 25)** (Rathelot and Strick, 2006) . Also, similar examination is also made between-limbs in a following study(Rathelot and Strick, 2009). In this study, the CM cells innervating fingers, elbow and shoulder are found to be overlapped, but at the same time, the CM cells innervating

elbow and shoulder localize superior to those of fingers **(Figure 26),** which is similar to the pattern of activation volume observed in fMRI study **(Figure14 and 15)**.

Therefore, it is reasonable to infer that the widely distributed and interleaved neural representations evoked by simple finger movements **(Figure 15)** as well as the less intermingled representation of elbow that localizes superior to the representation of fingers **(figure 15)**, represent the neuronal innervation of muscular synergies under simple movements.

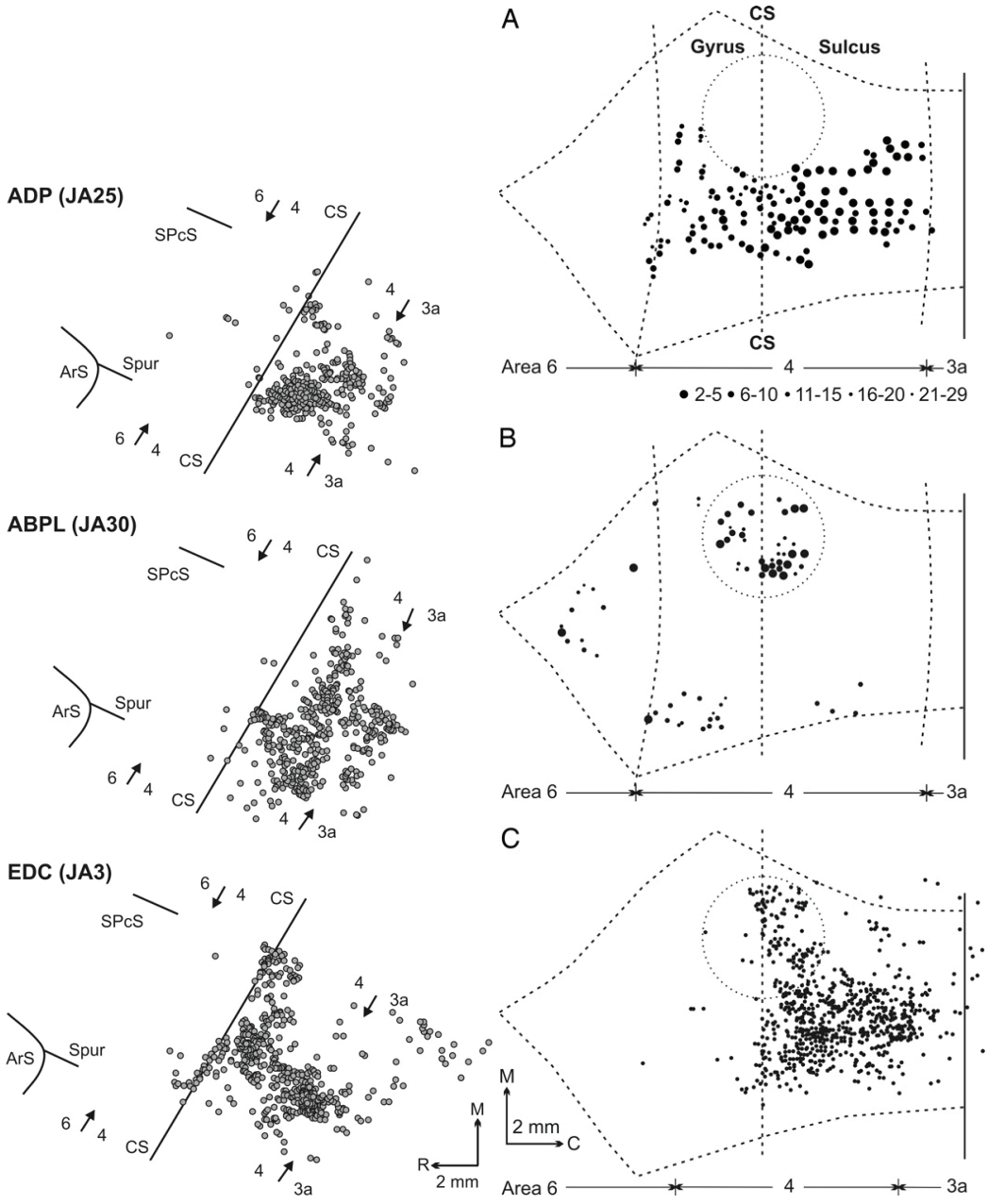


Figure 25. *Left:* Maps of the CM cells that innervate the motoneurons for digit muscles. *Right:* Maps of the cortical stimulation sites of digits (A) and shoulder (B) movements, and the spatial location of CM cells innervating digits on the same map (C). Revised from Rathelot (Rathelot, 2006). Abbreviations: ArS, arcuate sulcus; CS, central sulcus; M, medial; R, rostral; SPcS, superior precentral sulcus; ADP, adductor pollicis, ABPL, abductor

pollicis longus; EDC, extensor digitorum communis; JA3,JA25 and JA30 indicate three animals recruited in the experiment.

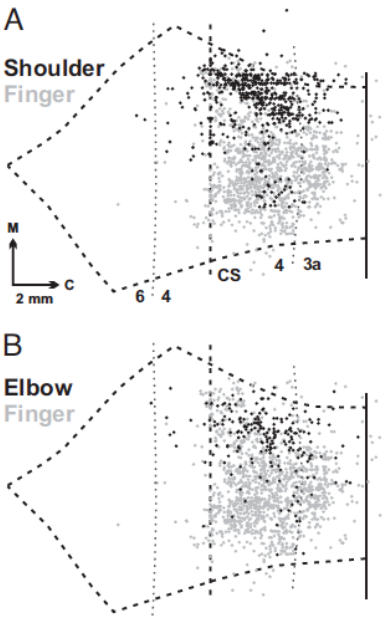


Figure 26. Overlaps map of CM cells innervating shoulder, finger and elbow muscles. Adopted from Rathelot (Rathelot and Strick, 2009). Abbreviations: CS, central sulcus; M, medial; C, caudal;

1.2 Representation of single finger movement in M1:neural basis of muscle synergy

The observation that representations of simple individual finger movements interleave in the small territories of area 4p (see figure 15) is consistent with the observation from histologic studies (Rathelot and Strick, 2006) that CM cells of single muscle intermingle, therefore indicating that the nature of these neural representations are related to direct control of muscles. Because single finger movements always involve the neuromuscular control of intrinsic muscle, extrinsic muscle (Schieber, 1995), as well as inevitable passive mechanical coupling (Lang and Schieber, 2004; Schieber, 1995), thus it is readily to presume that the volume overlapping of two fingers observed in fMRI study may be simply due to the recruitment of common extrinsic muscle and mechanical coupling.

However, even single M1 neuron innervate multiple muscles. There are two main different theories concerning how muscles are innervated in M1, one proposes that there is cortical efferent zones within which neurons that innervate a single motoneuron pool resides in a small region in M1(Asanuma and Rosén, 1972a) , and the other theory claims that there are overlapped colonies of cortical efferent in M1, also in which neurons innervates a single motoneuron pools concentrates (Andersen et al., 1975) .

if M1 represents individual muscle by sharply discrete cortical efferent zone (Asanuma and Rosén, 1972a) and the spatial volume overlapping we observed between separate finger movements should be due to the recruitment of the same muscle.

Indeed, mechanically, in both primate and human, the flexion and extension of single finger are largely dependent on the extrinsic muscles, for example, the flexor pollicis longus (FPL), and the flexor digitorum profoundus (FDP) that sends multiple tendons to four digits except thumb (Schieber, 1995)(Reilly and Schieber, 2003). An EMG study indicates that the flexion/extension of a single digit always facing the mechanical ‘connection’ of extrinsic muscles (Kilbreath and Gandevia, 1994). In this study, researchers record the EMG activity of FPL while guiding participant to flex (lift) the distal interphalangeal joint of other fingers. The result shows that the threshold lifting weight needed in producing EMG activity at FPL is very low for index finger (around 10% of maximum voluntary force) and much higher for little finger(around 10% of maximum voluntary force). Also, when recording from the index portion

of FDP and guiding subject to lift thumb, similarly, co-activation of FDP could been produced at low lifting weight on thumb. This indicates two facts, first, the independent flexion of thumb, index and little finger is very limited; second, co-activation of thumb extrinsic muscle (FPL) requires different efforts for index and little finger.

Thus, according the view of cortical efferent zone, one may expect different level of overlap of different finger pairs, for example, the RO between thumb and index movement should be different from the RO between thumb and little finger. However, the statistical results indicates identical RO% (Figure 24), thus M1 does not innervate single motoneuron pool by independent cortical efferent zones.

In primate, researches are in favor of the alternative 'overlapped colonies' control of motoneurons (Rathelot and Strick, 2006, 2009), some indirect evidence also indicate the existence of motor synergies in motor cortex and premotor which underlies muscular activity (Overduin et al., 2012) resembling the naturalistic muscular activity(Overduin et al., 2008) (Figure6-8).

However, with the result of this experiment, it is impossible to make direct inference that the activation volumes are the representation of muscular synergies used for each single movement, because of the mechanical limitation of independent single finger movement(Lang and Schieber, 2004) as well as the sluggish nature of fMRI signal(Logothetis et al., 2001).

2. Functional organization in parietal cortex

Plenty of researches in IPL indicated its involvement in action control (Rizzolatti et al., 1997) (Fogassi and Luppino, 2005)(Culham and Valyear, 2006). In primate, a map of intentional actions is found in parietal cortex(Andersen and Buneo, 2002). Simple movement is also important for skilled actions and coordinated actions. The somatotopic representation of action in IPL has been extensively investigated in physiological study of primate (Hyvärinen, 1981; Rozzi et al., 2008), and imaging studies of human (Buccino et al., 2001), with special interest for its role in action organization, observation and motor intention (Buccino et al., 2001; Fogassi and Luppino, 2005; Rizzolatti et al., 2001). These topics have been examined a lot in the literature by examining the neural responses of those actions such as grasping, kicking, chowing and reaching, which require cooperation of single movements of fingers, elbow, shoulder etc. However, it is still not clear that whether those simple movements are also represented in human parietal cortex.

In the fMRI study, we found a complete somatotopic map evoked by simple movements in IPL **(see table 6, figure 19)**. The repetitive movement of fingers, elbow, mouth and foot elicited neural responses concentrating in the most anterior and rostral region of IPL, which are assigned as PFt and PFcm subdivisions based their distinct architectonic characters (Caspers et al., 2006). The structure of this somatotopic map in IPL demonstrates some differences with that in M1 and S1.

First, single fingers are not represented in IPL, which implies the role of IPL in higher motor control compared to M1. This is consistent with the deficits of patients with parietal lesion that injury in IPL merely produces isolated motor deficits as in M1, but impairments related to spatial awareness(Mattingley et al., 1998), action organization(Sirigu et al., 1995), internal action representation (Sirigu et al., 1996) , motor intention(Sirigu et al., 2004) are observed with related patients.

Second, the arrangement of mouth, elbow, fingers and foot is not following their sequence of body parts in a strict order; double presentations of elbow are prominent in this map with one closer to mouth and finger. This implies that these neural representations evoked by simple movement might be arranged to serve the organization of action, thus, simple movements of different body parts which could corporate to form ethological actions are arranged closer in

terms of COG. The activation volumes of mouth, fingers and elbows in IPL supports this view. Different from M1, our result indicates the neural representation of mouth overlapped with those of fingers and elbow(Figure 22). This kind of arrangement could be seen in primate IPL, where the motor responses of actions related with mouth, hand, and more proximal limbs are distributed progressively from anterior to posterior in the convexity of IPL (Figure 28).

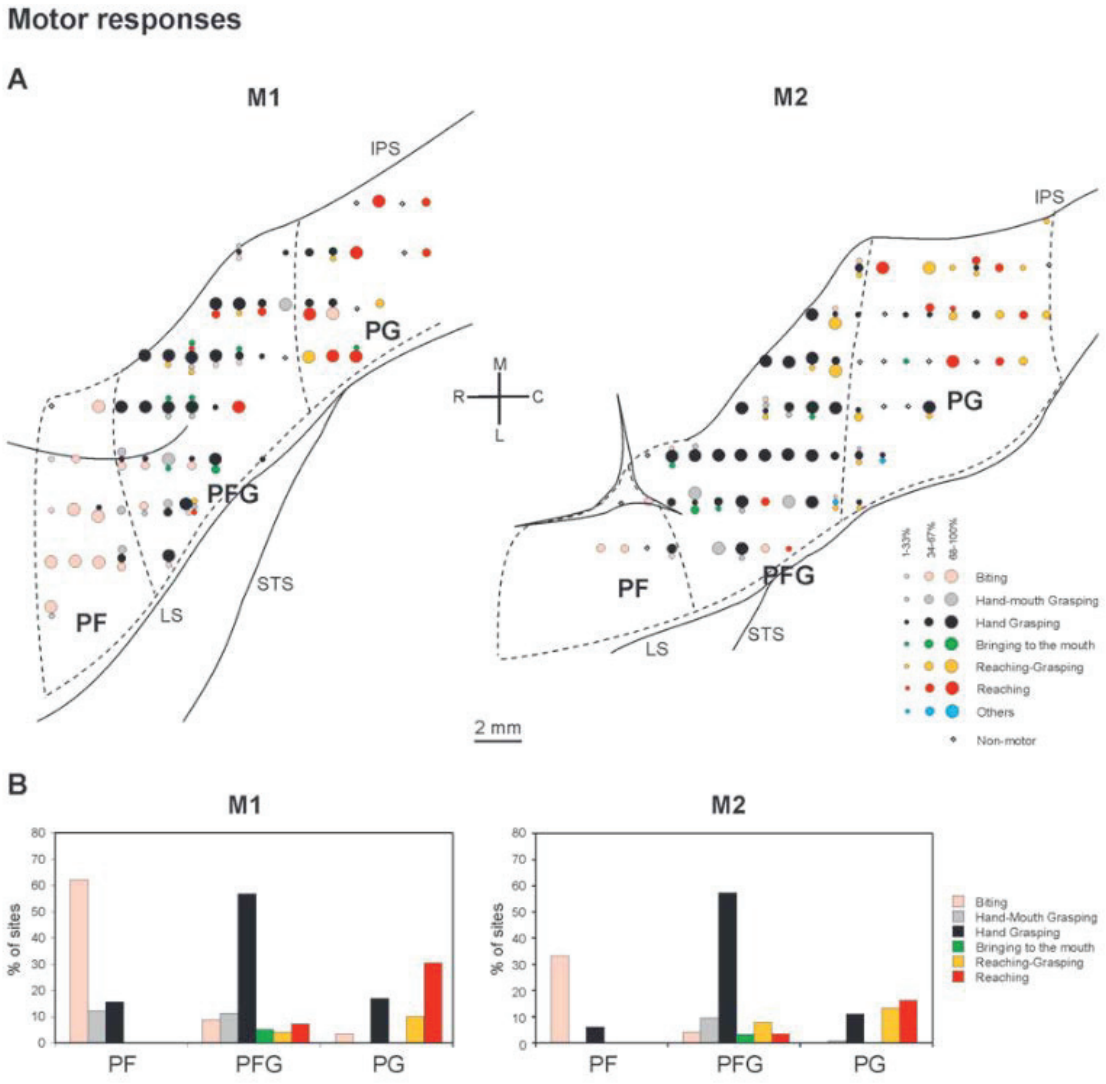


Figure 27. Neuronal representations of motor response in the convexity of IPL in primate. Different actions distributed along IPL. Adopted from (Rozzi et al., 2008) Abbreviations: IPS, intraparietal sulcus; LS, lateral sulcus; STS, superior temporal sulcus; M medial; L, lateral; R, rostral; C, caudal.M1 and M2 indicates two animals in this experiment.

The somatotopy of simple movement representation in IPL also sheds lights on the comparative difference between human and primate parietal cortex. Although the exact homologue of IPL between human and primate is not clear, our data doesn't support that PF and PG of primate IPL is approximately the homologue of those of human. Because in primate, simple non-object related actions could not evoke any motor- or sensory responses in primate IPL, this resembles our finding in human SPL (Hyvärinen, 1981; Rozzi et al., 2008).

Intuitively, one may ask the question that what are the nature of the neural responses evoked by simple movements in rostral IPL, PFt, PFcm and PFop (Figure 28)? Variant functions have been found in human IPL, such as that DES evokes motor intention in human PPC(Desmurget et al., 2009), action observation also elicits neural response in IPL (Buccino et al., 2001).Such complexity of function has not been well coupled with advanced anatomical subdivisions.

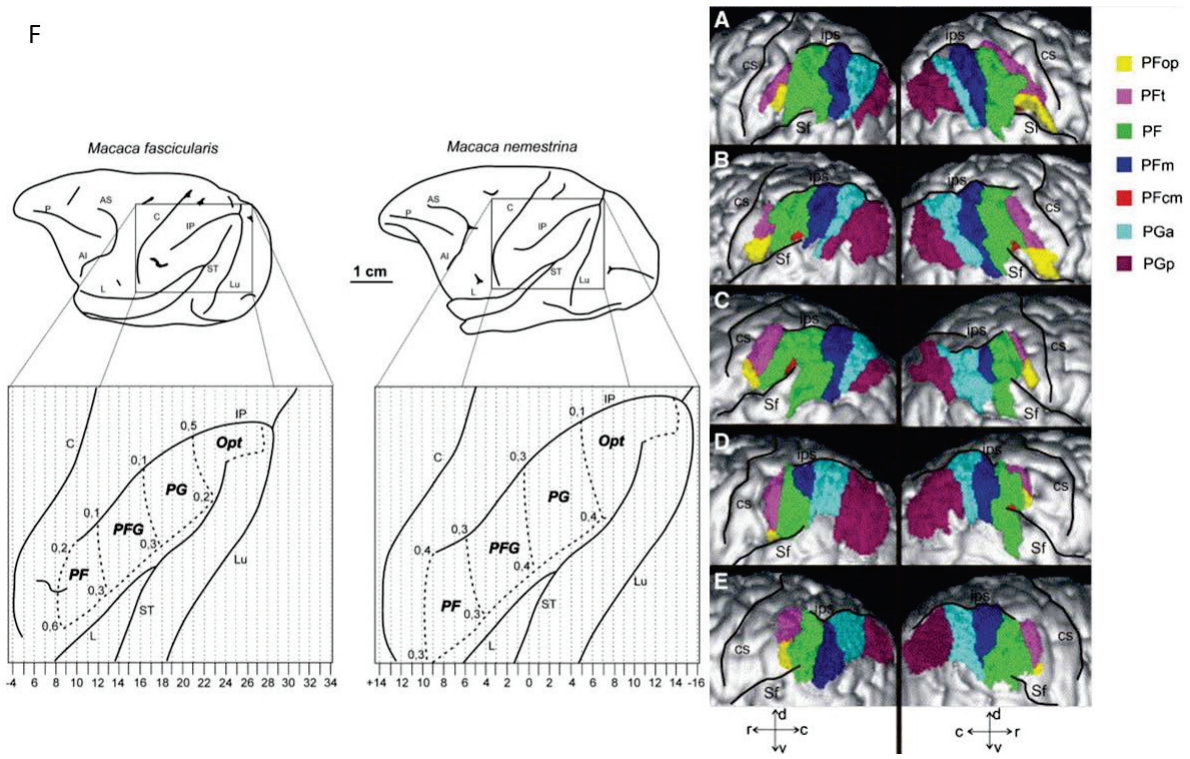


Figure 28. The architectonic subdivision of IPL in human (A-E) (Caspers et al., 2006) and in monkeys (F)(Gregoriou et al., 2006).

In fact, neuronal responses recorded in primates indicates that it is sensory response (Hyvärinen, 1981) and concentrates in the rostral portion of IPL in a somatotopic manner (Rozzi et al., 2008). Thus, the neural responses we observed in this fMRI study could be either motor responses or sensory feedback.

Motor system has been found to be less serially organized than previously hypothesized (Georgopoulos, 1991), because of its the complex intra-cortical connections (Wise et al., 1997). In primate, the connectivity of area PF provides the anatomical basis for the somatosensory map in this region, indicating its possible role in sensorimotor transformation, especially in guiding the the movement of mouth and hand.

In an early series studies by Petrides and Pandya, the anterior most regions in IPL, area PF, was found to have connection with post central gyrus (area 2) (Pandya and Seltzer, 1982) parietal

opercular regions and the ventral area 6 and ventral area 46 of rhesus monkey (Petrides and Pandya, 1984). Rozzi and colleagues further systematically examine the cortical connection of IPL in macaque monkey with a histological l procedure in the beginning of the experiments on same monkeys to parcellate the IPL to four cytoarchitectonic subdivisions-area Opt, PG, PFG and PF (Rozzi et al., 2006). By retrograde labeling, they found the most dense and confined connections of PF are to the ventral part of area 2 and SII region in the parietal operculum, relative week labeling is with ventral F5 and area 46 in the frontal cortex. Considering the connection with frontal motor regions, in particular with the premotor cortex, Gregoriou and colleagues found that these four subdivisions of IPL project to premotor cortex in different ways, with ventral premotor mostly connects with area PF and dorsal PM mostly connect with area Opt (Gregoriou et al., 2006). Also, within the posterior parietal cortex, PF is also connected with somatosensory face area VIP(Colby et al., 1993) and hand area AIP (Murata et al., 2000).

In summary, the cortical connections of PF with SI, SII and PM regions and the 'feedback' and feedforward' laminar distribution of these projections(Gregoriou et al., 2006) in primate provide the anatomical basis of its somatosensory map and imply its role in sensorimotor transformation, particular for mouth and hand movement.

In human, systematic evidence involving both the function and connection of the anteriormost regions in IPL that are probably the homologues of primate PF, has not been provided. In this fMRI study, we show that a complete functional somatotopic map of mouth, fingers(hand), elbow and foot could be found covering the human PFt and PFcm regions (Figure 22). Thanks to recent progress of imaging technique and computational method, evidence on human cortical connection shed light on the question I brought up early, what is the nature of this somatotopic map in human. Eickhoff's team examined the anatomical connectivity of parietal opercula areas having cytoarchitectonic distinctions, and discovered in human a white matter pathway between the OP1 and the anterior IPL (Eickhoff et al., 2010). What's more, in human, area OP4 has been confirmed to have somatotopic representations of contralateral body when tactile stimulation to the skin is applied at face, hands, trunk and legs (Eickhoff et al., 2007b). Therefore, the anterior IPL-OP1 network could serve the higher order somatosensory processing.

III.2 Motor intention and motor preparation

Our data show that there is no significant difference, on average, between the time required to initiate a movement in response to a visual cue ($RT_{/ext}$) and the time required to initiate the same movement in response to an internal intention to act ($RT_{/int}$). This observation does not support the claim that conscious intention to act emerges in response to the neural activity mediating motor preparation (Haggard, 2005; Hallett, 2007; Miller et al., 2011). Although our data could be compatible with the alternative view that a conscious intention to act triggers motor preparation, at least in the context of Libet's protocol (Desmurget, 2013; Desmurget and Sirigu, 2009; Fried et al., 2011), they do not directly support this idea. It could be, for instance that these two processes are largely parallel, as could be suggested by the theory of distinct pathways for perception and action(Castiello et al., 1991; Goodale and Milner, 1992). With respect to this point, one should acknowledge that our inability to identify a significant difference between $RT_{/int}$ and $RT_{/ext}$ could reflect a lack of statistical power (Rohenkohl et al., 2011). However, even if this is the case, the magnitude of the difference we observed between RTs seems too small (9 ms) to be compatible with the results of EEG studies suggesting that RP (considered as a marker of motor preparation) precedes the emergence of motor preparation by several hundreds of milliseconds (Haggard and Eimer, 1999; Libet et al., 1983).

The absence of a causal link from motor preparation to conscious intention is consistent with a recent study showing that motor intentions can arise independently of motor preparation in humans (Desmurget and Sirigu, 2012). Following electrical stimulation of the inferior parietal lobule (IPL) during awake brain surgeries (BA 39-40), patients report conscious intentions to move or talk. These intentions are formulated in very broad and general terms ("a will to move the chest" or "a desire to move the foot") and the patients do not spontaneously describe the exact movement they want to perform. When prompted to do so, they report that they "don't know" which, clearly, would not be expected in a conceptual framework where movement intention results from the unconscious neural processes mediating the planning of a specific motor response. Strikingly, such an accurate description of the movement to be performed arises in response to sub-motor-threshold stimulations of the supplementary motor area (SMA)(Fried et al., 1991). In this case, the subjects report compulsive urges to move "the right leg inward" or "the right thumb and index finger". In contrast to what is observed following parietal

stimulations, when the intensity of the stimulation is slightly increased, the intended movement actually occurs. In light of these observations, it has been suggested that conscious intentions in IPL are related to the initial selection of a motor response not yet planned, whereas the urges to move in SMA are associated with the release of inhibition that occurs in this region when the intended movement has been planned and is ready to be performed(Ball et al., 1999; Desmurget and Sirigu, 2009, 2012).

These data seem consistent with recent observations that challenge Libet's original assumption that the readiness potential (RP) is an early marker of motor preparation (Desmurget, 2013; Desmurget and Sirigu, 2009; Fried et al., 2011; Guggisberg and Mottaz, 2013). Anatomically, the medial prefrontal region, and more precisely the SMA, is thought to be the main source of RP (Eimer, 1998; Ikeda et al., 1992). In patients with lesions of IPL, the motor part of Libet's task (i.e. pressing the button and estimating the time of button press) is correctly executed although no RP is observed(Sirigu et al., 2004). In the same way, in healthy humans, RP has been associated with the process of paying attention to the timing of movement(Baker et al., 2012) or the rotating clock (Miller et al., 2011). It emerges whether the subjects plan a movement or not (Herrmann et al., 2008; Trevena and Miller, 2010). This latter observation seems in line with recent computational data indicating that the gradual buildup of RP prior to initiation of self-initiated movements could be mostly artifactual and related to flucutations of neural activity (Jo et al., 2013; Schneider et al., 2013).

At a more "philosophical" level, it has been suggested that free will is a mere illusion because we only become aware of our intention to move after the desired action has already been planned in our brain (Haggard, 2005, 2008; Wegner, 2003). Our data challenge this claim, at least in the context of Libet's paradigm. Indeed, we have shown that the actual implementation of a simple motor response does not precede the conscious intention of performing this action. This does not mean, of course, that unconscious processing are not involved in the emergence of a conscious intention to do something(Bargh et al., 2012; Dijksterhuis and Bargh, 2001; Jahanshahi et al., 1992). However, this challenges the common view that we become aware of our intention to act during the course -and as a result of- motor preparation.

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